Guide to Microbicide Research and Development

e

HIV Infection

Selected Bibliography

through

September 1996

e

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion
Division of Reproductive Health
National Center for HIV, STD, and TB Prevention
Division of HIV/AIDS Prevention
Atlanta, GA 30333

TABLE OF CONTENTS

Introduction

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) represent a growing public health concern. HIV infection becomes a major cause of morbidity and death among American women of reproductive age. In 1994, HIV infection became the leading cause of death of Americans aged 25–44 years, the fourth leading cause of death of women and the leading cause of death of black women in this age group.[1] The proportion of AIDS cases in U.S. adult and adolescent females has nearly tripled, from 7% of cases reported in 1985 to 20% of cases reported in 1996.[2]

In 1995, heterosexual contact became the leading cause of HIV transmission among women in the United States and continues to increase in importance;[3] it accounts for more than 80% of HIV infections worldwide.[4] Particularly at risk are women and adolescent girls whose heterosexual partners engage in high–risk behaviors, those with multiple sex partners, and those with other sexually transmitted diseases (STDs).

The World Health Organization has estimated that more than 125 million new cases of STDs occur each year.[5] In 1995, CDC received reports of 392,848 cases of *Neisseria gonorrhoeae*, 477,638 cases of *Chlamydia trachomatis*, and 16,500 cases of primary and secondary syphilis.[6] Some STDs, especially in women, may be asymptomatic, and untreated STDs can cause infertility, ectopic pregnancy and other complications, chronic pelvic pain, cervical neoplasia, and other serious sequelae. Moreover, the presence of other STDs can increase the risk of acquiring HIV.[7]

To reduce sexually transmitted infection by HIV and other STDs among women, current public health efforts emphasize consistent and correct condom use and counseling that supports decisions to reduce sexual risk behaviors. For a woman, because personal, social, and cultural factors may interfere with her ability to have her partner use male condoms during sexual intercourse, other protective methods are needed. In addition, because many women at risk for sexually transmitted HIV and STDs may also want to have children, the development of disease prevention methods that do not prevent pregnancy is warranted.

One alternative to male condoms may be microbicides that women could administer vaginally to protect themselves from infection with HIV and other STDs. Microbicides may also prove to be useful in preventing HIV and other STDs for other populations who do not use condoms, including men who have sex with men. To date, no product has been approved for use as a microbicide against sexually transmitted HIV or other STD pathogens for vaginal or rectal use in the United States. Although some spermicides labeled and marketed as contraceptives in the United States may be used to prevent the transmission of HIV and other STDs, none has been approved for HIV or STD prevention in the United States.

The *Guide to Microbicide Research and Development* is a comprehensive bibliography intended as a resource for clinicians, researchers, and public health and prevention specialists interested in microbicides. It contains more than 250 abstracts summarizing past research and policy on products intended to prevent HIV and STD through vaginal or anal intercourse, including preclinical studies (defined as studies in laboratory and animal models) and clinical studies (defined as studies of safety, dosage, and toxicity among a small number of human volunteers [Phase I]; studies of dosage, toxicity, and adverse effects among a larger number of volunteers [Phase II]; and efficacy studies among large numbers of volunteers [Phase III]. It also includes reports on behavioral research, review articles, and policy papers. Because some spermicides that are effective for pregnancy prevention may be effective in preventing HIV infection, some abstracts refer to spermicides as microbicides.

Publication content and organization

The bibliography contains five sections: preclinical studies, clinical studies, behavioral studies, review articles, and policy papers. The compilers listed a report that addresses more than one of these five subject areas in the section that is the focus of the report and listed the title and authors in related sections. Each report is also indexed by title and all authors.

Each report includes the report number, title, form of report (e.g., journal article, letter), authors, publication source, and one of three types of abstracts: a published abstract, an authors' abstract, or an annotators' abstract; for a few reports, a brief commentary to clarify the subject of the report is given. Published abstracts were taken from electronic databases and thus may be reproduced without copyright release from the authors. Authors' abstracts were not taken from electronic databases but were included in the bibliography with the authors' permission. Annotators' abstracts were written by the compilers when a published or an author's abstract was not available.

Sample Abstract

II.C.i.a–2

The alphanumeric code indicates that this item is listed in the section titled "Clinical Studies [II] of Effectiveness © Against STD [I]–Nonoxynol–9 [a]," second report in this section (2). Note that the final digit of the alphanumeric code is not included in the online version.

A Case–Control Study of Spermicides and Gonorrhea.

Form: Journal Article.
Author: Austin, H.; Louv, W. C.; Alexander, W. J.
Source: JAMA. 251(21):2822–24, June 1, 1984.

Published Abstract: A case–control study was done to evaluate the effectiveness of vaginal spermicides as a prophylaxis against gonorrhea. Subjects included 735 women with gonorrhea and 958 controls seen in a sexually transmitted disease clinic. The relative risk (RR) of gonorrhea for spermicide users compared with nonusers was 0.67 (90% confidence interval [CI] 0.44 to 1.0). After the exclusion of women who were using oral contraceptives or an intrauterine device or who had a tubal ligation, the RR was 0.47. The protective effect of spermicides was confined largely to women who had also used diaphragms or whose partners had used condoms. The RR of gonorrhea for spermicide and condom users relative to nonusers of spermicides, condoms, and diaphragms was 0.41 (90% confidence limits, 0.21 to 0.79), while for spermicide and diaphragm users, this RR was 0.45 (90% confidence limits, 0.15 to 1.3). These results suggest that a woman can appreciably decrease her risk of contracting gonorrhea if she uses spermicide in conjunction with either the diaphragm or the condom.

Methods Used to Compile the Bibliography

Compilers electronically searched public health, medical, mental health, and social sciences journals written in English that were indexed in the electronic databases MEDLINE and Current Contents (1976 through 1996), using keywords in summaries or titles. Articles written in other languages but published with English abstracts were not included. For 1985 through 1996, compilers searched the keywords anal intercourse, antiinfective agents, antiviral agents, bacterial vaginosis, *Chlamydia trachomatis*, clinical studies, condoms, female, human immunodeficiency virus, human papillomavirus, intravaginal administration, lactobacillus, male, microbicides, *Neisseria gonorrhoeae*, pelvic inflammatory disease, preclinical studies, rectum, sexually transmitted diseases, spermicides, vagina, and the following active ingredients: benzalkonium chloride, carageenan, chlorhexidine, curdan sulfate, detergents, dextran sulfate, gossypol, gramicidin, heparin sulfate, menfegol, nonoxynol, octoxynol, povidone iodine, and reverse transcriptase inhibitors. For 1976 through 1984, compilers searched the same keywords, but

limited the active ingredients search to nonoxynol–9, octoxynol, and povidone iodine**.** Behavioral studies were identified by electronically searching PSYCLIT, a behavioral science electronic database, for the period 1988 through 1996; the keywords searched were acceptability, female, intravaginal administration, microbicide, spermicide, and vagina.

Compilers also traced references in reports identified through electronic searches. A few reports on biomedical topics of historical significance that were identified by reference tracing and that were published before 1976 are also included.

Reports that address male and female condoms used without spermicides, contraceptive efficacy of spermicides, treatment of STDs, and microbicides for oral administration were not included. Reference tracing was used to search books, monographs, and other materials not found in electronic databases.

How to obtain this publication

An electronic copy of the *Guide* is available through the Internet on the World Health Organization/UNAIDS World Wide Web site at http://www.who.org/programmes/WHOProgrammes.html.

How to obtain more information

For more information about a specific report, contact the author or agency responsible for the report.

If you need more information about bibliography contents or wish to submit new materials for inclusion in the online version, contact:

John Kromodimedjo
UNAIDS
20 Avenue Appia
CH–1211 Geneva 27
Switzerland
E–mail: kromodimedjoj@who.ch
+41 22 791 4737

For inquiries about product development and approval in the United States:

Food and Drug Administration
Division of Antiviral Drug Products (HFD–530)
Nicholson Research Center, 2nd Floor
5600 Fishers Lane
Rockville, MD 20857
(301) 443–9553
http://www.fda.gov

References

1. Centers for Disease Control and Prevention. “Update: Mortality Attributable to HIV Infection Among Persons aged 25–44 years—U.S, 1994,” *Morbidity and Mortality Weekly Report*. 45(6): February 16, 1996.
2. Centers for Disease Control and Prevention, National Center for HIV, STD, and TB Prevention (NCHSTP). *HIV/AIDS Surveillance Report*. 8(2), 1996.
3. Centers for Disease Control and Prevention. “Heterosexually Acquired AIDS—United States,” *Morbidity and Mortality Weekly Report*. 43(9):155-60, 1994.
4. International Working Group on Vaginal Microbicides. “Recommendations for the Development of Vaginal Microbicides,” *AIDS: Special Report*, 10, 1996.
5. Alexander, N. J. “Barriers to Sexually Transmitted Diseases.” *Scientific American*, *Science of Medicine*. 3(2):32–41; March/April 1996.
6. Centers for Disease Control and Prevention, Division of STD Prevention (DSTDP). *Sexually Transmitted Disease Surveillance*. September 1995.
7. Grosskurth,H.; Mosha, F.; Todd, J.; et al. "Impact of Improved Treatment of Sexually Transmitted Diseases on HIV Infection in Rural Tanzania: Randomised Controlled Trial," *Lancet* . 346(8974):530, August 26, 1995.

I.A.*i*. Preclinical Studies of Detergent Microbicides–Nonoxynol–9.

I.A.i–1
Inactivation of Herpes Simplex Viruses by Nonionic Surfactants.

Form: Journal Article.
Author: Asculai, S. S.; Weis, M. T.; Rancourt, M. W.; Kupferberg, A. B.
Source: Antimicrobial Agents and Chemotherapy. 13(4):686–690, April 1978.

Authors' Abstract: The authors demonstrate that nonionic surface–active agents possessing ether or amide linkages between the hydrophilic and hydrophobic portions of molecules rapidly inactivate the infectivity of herpes simplex viruses. This activity stems from the ability of nonionic surfactants to dissolve lipid–containing membranes. This was confirmed by observing surfactant destruction of mammalian cell–plasma membranes and herpes simplex virus envelopes. Proprietary vaginal contraceptive formulations containing nonionic surfactants also inactivated herpes simplex virus infectivity. This observation suggests that nonionic surfactants in appropriate formulation could effectively prevent herpes simplex virus transmission.

I.A.i–2
The Prophylactic Properties of the Today Sponge and Other Spermicide–Containing Contraceptives.
Author: Berger, K. L.; Remington, K.
[See abstract IV.A–3.]

I.A.i–3
Comparative In Vitro Study of Contraceptive Agents With Anti–HIV Activity: Gramicidin, Nonoxynol–9, and Gossypol.

Form: Journal Article.
Author: Bourinbaiar, A. S.; Lee–Huang, S.
Source: Contraception. 49(2):131–137, February 1994.

Published Abstract: Gramicidin, a polypeptide antibiotic derived from *Bacillus brevis*, was compared in vitro with the established contraceptive virucidal agents, nonoxynol–9 and gossypol, for activity against human immunodeficiency virus (HIV) infection. The effective antiviral concentration of gramicidin required for complete HIV inactivation was 1,000–fold greater than the doses required for either nonoxynol–9 or gossypol. The authors recommend that gramicidin, routinely used as a contraceptive agent in the former Soviet Union, should be considered for in vivo trials.

I.A.i–4
New and Existing Spermicides With Virucidal Properties.
Author: Chantler, E. N.
[See abstract IV.A–7.]

I.A.i–5
Activity of Nonoxynol–9 Against *Chlamydia trachomatis*.

Form: Journal Article.
Author: Ehret, J. M.; Judson, F. N.
Source: Sexually Transmitted Diseases. 15(3):156–157, July–September 1988.

Published Abstract: None.
Annotators' Abstract: Four in vitro studies of the activity of nonoxynol–9 against *Chlamydia trachomatis* are reviewed. The authors discuss inconsistencies in inclusion staining, measures of cytotoxocity, and timing of exposure to nonoxynol–9. The authors call for clinical trials to test the efficacy of nonoxynol–9 against *C. trachomatis* because of the inconsistency and difficulty of interpreting results of in vitro testing.

I.A.i–6
The Spermicide Nonoxynol–9 Does Not Inactivate Papilloma Virus.

Form: Journal Article.
Author: Hermonat, P. L.; Daniel, R. W.; Shah, K. V.
Source: Sexually Transmitted Diseases. 19(4):203–205, July–August 1992.

Published Abstract: Vaginal spermicides are effective contraceptives, and are also capable of inactivating many sexually transmitted pathogens by their detergent effect on bacterial cell membranes and viral envelopes. A 5% concentration of nonoxynol–9, the most

frequently used active ingredient of spermicides, was tested for its ability to reduce the transforming activity of bovine papilloma virus type 1 (BPV–1) and the infectivity of BK virus (BKV) and cytomegalovirus (CMV). Nonoxynol–9 markedly reduced the infectivity of CMV, an enveloped virus, but did not significantly affect the activity of the nonenveloped viruses BPV–1 and BKV. Human papilloma viruses (HPV) are nonenveloped viruses, and papilloma virus infections are strongly implicated in the etiology of cervical cancer. The authors conclude that the reported protective effect of vaginal spermicides against cervical cancer is very likely not mediated by direct inactivation of papilloma viruses by the spermicide.

I.A.i–7
Nonoxynol–9: Differential Antibacterial Activity and Enhancement of Bacterial Adherence to Vaginal Epithelial Cells.

Form: Journal Article.
Author: Hooton, T. M.; Fennell, C. L.; Clark, A. M.; Stamm, W. E.
Source: Journal of Infectious Diseases. 164(6):1216–1219, December 1991.

Published Abstract: The antibacterial activity and adherence–enhancing effects of nonoxynol–9 were evaluated against vaginal and uropathogenic bacteria. Results indicated that nonoxynol–9 was markedly less active against the 43 uropathogenic bacterial and yeast strains tested (minimum inhibitory concentration for 90% of the strains (MIC_{90}) > 32%) than against the 26 *Gardnerella vaginalis* strains (MIC_{90} # 0.015%) and the 53 *Lactobacillus* strains (MIC_{90}, 8%). Hydrogen peroxide–producing strains of *Lactobacillus* were more susceptible to nonoxynol–9 (MIC_{90}, 4%) than nonproducers (MIC_{90}, 16%). Two *Escherichia coli* strains that expressed type 1 fimbriae and three *Lactobacillus* strains adhered in significantly higher numbers to vaginal epithelial cells preincubated with 5% nonoxynol–9 than to control cells preincubated with phosphate–buffered saline. In conclusion, spermicides may provide a selective advantage in colonizing the vagina with nonoxynol–9–resistant uropathogens, such as *E. coli*, via a reduction in vaginal lactobacilli (especially the hydrogen peroxide–producing strain). This may also be accomplished through enhancement of adherence of *E. coli* to epithelial cells.

I.A.i–8
The Inhibitory Effect of Spermicidal Agents on Replication of HSV–2 and HIV–1 In Vitro.

Form: Journal Article.
Author: Jennings, R.; Clegg, A.
Source: Journal of Antimicrobial Chemotherapy. 32(1):71–82, July 1993.

Published Abstract: Five spermicides, including nonoxynol–9, were assessed for their inhibitory activity against herpes simplex virus type 2 (HSV–2) and human immunodeficiency virus type 1 (HIV–1). A further eight commercially available spermicidal preparations containing varying concentrations of either nonoxynol–9 or nonoxynol–11 were also assessed for activity against HSV–2. All spermicides and spermicidal preparations tested showed inhibitory activity against both viruses over periods of time ranging from 30 seconds to 5 minutes. This activity was dependent on the concentration to which the viruses were exposed.

Commentary: Commercially available spermicidal compounds containing differing concentrations of nonoxynol–9 or nonoxynol–11 were assessed for activity against HSV–2, and four spermicides—nonoxynol–9 (8%), benzalkonium chloride (3%), menfegol (2%), and sodium decussate (2%, 3%, and 5%)—were tested against HIV–1.

I.A.i–9
Efficacy of Glove Combinations in Reducing Cell Culture Infection After Glove Puncture With Needles Contaminated With Human Immunodeficiency Virus Type 1.

Form: Journal Article.
Author: Johnson, G. K.; Nolan, T.; Wuh, H. C.; Robinson, W. S.
Source: Infection Control and Hospital Epidemiology. 12(7):435–438, July 1991.

Published Abstract: Objective: The authors studied the effect of various latex and treated glove combinations in reducing the frequency of human immunodeficiency virus (HIV) infection of tissue culture cells after puncture by surgical

needles contaminated with infectious human immunodeficiency virus type 1 (HIV–1). Design: One, two, or three layers of sterile latex glove material, or two latex layers with intermediate cotton or Kevlar (with or without the virucidal compound nonoxynol–9) were used to cover 24 well–cell culture dishes containing MT2 cells in cell culture medium. Surgical needles wet with cell culture medium containing HIV–1 (human T–lymphotropic virus (HTLV) IIIA strain) were passed through the glove materials into the culture medium in the wells of the culture dishes. The culture medium in each well was then assayed biweekly for HIV–1 p24 antigen as a test for infection of cells in the well. The rate of HIV–1 infection of cell cultures after glove puncture was greater than 90% with a single latex surgical glove barrier; 23%–60% with double or triple layers of latex gloves; < 8% with an intermediate cotton glove impregnated with 4% nonoxynol–9; 6% with an intermediate Kevlar glove; and 0% with an intermediate Kevlar glove impregnated with nonoxynol–9. Results show that an intermediate glove of Kevlar, or of Kevlar or cotton impregnated with virucidal compound nonoxynol–9 between standard latex gloves, may improve surgical glove safety, compared with latex gloves alone with respect to needlestick transmission of HIV–1. The experimental model used may permit rapid investigation of other glove systems as barriers to the transfer of infectious agents through gloves by needlestick.

I.A.i–10

The Susceptibility of Organisms Associated With Bacterial Vaginosis to Spermicidal Compounds, In Vitro.

Form: Journal Article.
Author: Jones, B. M.; Willcox, L. M.
Source: Genitourinary Medicine. 67(6):475–477, December 1991.

Published Abstract: Objectives: Bacterial vaginosis (BV) is a prevalent vaginal infection that is now regarded as a risk factor in more serious pelvic and obstetric complications. Because spermicides are known to have antimicrobial activity against other sexually transmitted diseases, this study was to test whether the causative organisms of BV were also susceptible to spermicides in vitro. Location was at the Department of Experimental and Clinical Microbiology, University of Sheffield Medical School, United Kingdom. Design: Minimum inhibitory concentrations (MICs) of five spermicidal compounds were determined for the organisms associated with BV using an agar dilution technique. Nonoxynol–9, nonoxynol–11, docusate sodium, benzalkonium chloride, and menfegol were tested against 20 strains each of *Gardnerella vaginalis*, *Bacteroides*, and *Mobiluncus* organisms isolated from patients with BV who attended the Department of Genitourinary Medicine, the Royal Hallamshire Hospital, Sheffield. The main outcome measure was the susceptibility of in vitro BV–associated organisms to spermicidal compounds. Results: *G. vaginalis*, *Mobiluncus* species, *Bacteroides bivius*, and *Bacteroides disiens* were all found to be susceptible to the five spermicides tested, with MICs ranging between #19 and 5,000 mg/L (0.0019%–0.5%). Conclusion: The concentrations of spermicides incorporated in contraceptive preparations are usually between 3% and 8%, which is far in excess of the MICs found for BV organisms. Their usage could exert a significant antimicrobial effect and be a useful prophylactic in preventing BV.

I.A.i–11

In Vitro Evaluations of Condoms With and Without Nonoxynol–9 as Physical and Chemical Barriers Against *Chlamydia trachomatis*, Herpes Simplex Virus Type 2, and Human Immunodeficiency Virus.

Form: Journal Article.
Author: Judson, F. N.; Ehret, J. M.; Bodin, G. F.; Levin, M. J.; Rietmeijer, C. A.
Source: Sexually Transmitted Diseases. 16(2):51–56, April–June 1989.

Published Abstract: Simulated in vitro intercourse conditions demonstrated that unlubricated latex condoms provide an effective physical barrier to high concentrations of *Chlamydia trachomatis*, herpes simplex virus type 2, and human immunodeficiency virus (HIV). Since condoms can be damaged after manufacturing inspection and prior to use, latex condoms alone should not be perceived as absolute protection against sexually transmitted diseases. Nonoxynol–9 used in conjunction with condoms provided additional, yet still not foolproof, protection against the three viruses.

Commentary: In this study, at concentrations of 0.01 to 0.00001 mg/ml, nonoxynol–9 inactivates

herpes simplex virus with 2,000 plaque–forming units (PFUs) per 2 ml of medium. A comparison was made of 10 condoms with lubricant only and 10 condoms with 6.6% nonoxynol–9 in a polyethylene glycol vehicle in a test that ruptured the condoms. After rupture, HIV was detectable in 7 of 10 condoms without nonoxynol–9 and in none of the 10 condoms with nonoxynol–9.

I.A.i–12
Effects of the Spermicidal Agent Nonoxynol–9 on Vaginal Microbial Flora.
Author: Klebanoff, S. J.
[See abstract I.F–5.]

I.A.i–13
In Vitro Activity of Nonoxynol–9 on McCoy Cells Infected With *Chlamydia trachomatis*.

Form: Journal Article.
Author: Knight, S. T.; Lee, S. H.; Davis, C. H.; Moorman D. R.; Hodinka, R. L.; Wyrick, P. B.
Source: Sexually Transmitted Diseases. 14(3):165–173, July–September 1987.

Published Abstract: Nonoxynol–9, a nonionic detergent and active ingredient in spermicidal contraceptives, has been reported to have anti–chlamydia properties. However, in this study, exposure of elementary bodies of *Chlamydia trachomatis serovar E* to nonoxynol–9 (12.5–10,000 micrograms/ml) had no effect on chlamydial infectivity. In contrast, uninfected McCoy cells exposed to increasing concentrations of nonoxynol–9 over 72 hours displayed dose–related cytotoxicity. When infected McCoy cells were exposed to nonoxynol–9, the developing chlamydial inclusions did not stain with iodine even though they were similar in number and appearance to the inclusions in unexposed, infected monolayer. Electron microscopy of infected cells treated with nonoxynol–9 revealed apparent damage to the inclusion membrane and reticulate bodies within. The infectivity of the chlamydiae in the iodine–negative inclusions on subpassage was only 0.3%. The authors conclude that the primary action of nonoxynol–9 is on the McCoy cell and that there may be secondary effects on the intracellular parasite.

I.A.i–14
Inactivation of HIV by Nonoxynol–9.

Form: Journal Article, Letter.
Author: Malkovsky, M.; Newell, A.; Dalgleish, A. G.
Source: Lancet. 1(8586):645, March 19, 1988.

Published Abstract: None.
Annotators' Abstract: This letter reports in vitro activity of nonoxynol–9 against human immunodeficiency virus (HIV). Using different assay systems and viral isolates, it was demonstrated that formulations containing varying amounts of nonoxynol–9 inactivate HIV at concentrations between 0.1% and 1.0% (vol/vol). Assuming that the nonoxynol–9 formulations would not be diluted more than 100 times during their in vivo application, the authors conclude that these currently available formulations may be effective in preventing HIV transmission during sexual intercourse.

I.A.i–15
Effect of Virus Dose and Nonoxynol–9 on the Genital Transmission of SIV in Rhesus Macaques.

Form: Journal Article.
Author: Miller, C. J.; Alexander, N. J.; Sutjipto, S.; Joye, S. M.; Hendrickx, A. G.; Jennings, M.; Marx, P. A.
Source: Journal of Medical Primatology. 19(3–4):401–409, 1990.

Published Abstract: One inoculation of cell-free simian immunodeficiency virus from the macaque (SIVmac) (50 median tissue culture infective doses ($TCID_{50}$)) caused persistent viremia in 9 of 13 female rhesus macaques inoculated intravaginally. Persistent viremia was produced in two of four male rhesus macaques by placing cell-free SIVmac (50 $TCID_{50}$) onto the skin and urethral of the penis. Placing a spermicide containing nonoxynol-9 (vaginal foam at 12.5% vol/vol) into the vaginal canal prior to repeated intravaginal inoculations of SIV prevented transmission of the virus in three of six female rhesus macaques.

I.A.i–16
The Cat/Feline Immunodeficiency Virus Model for Transmucosal Transmission of AIDS: Nonoxynol–9 Contraceptive Jelly

Blocks Transmission by an Infected Cell Inoculum.

Form: Journal Article.
Author: Moench, T. R.; Whaley, K. J.; Mandrell, T. D.; Bishop, B. D.; Witt, C. J.; Cone, R. A.
Source: AIDS. 7(6):797–802, June 1993.

Published Abstract: Feline immunodeficiency virus (FIV), a lentivirus similar to human immunodeficiency virus (HIV), causes a disease similar to acquired immunodeficiency syndrome (AIDS) in domestic cats. HIV is transmitted primarily across mucosal surfaces, and infected cells may be important in this transmission. To develop an animal model to study transmucosal lentivirus transmission and determine whether topical application of contraceptive jelly can block transmission by an infected cell inoculum, the authors tested the ability of FIV–infected cells to transmit infection across the vaginal, rectal, and oral mucosa of the cat, and whether a vaginal contraceptive jelly could prevent such transmission. An inoculum consisting of 2 million FIV–infected primary cat T cells was administered vaginally, rectally, or orally to female cats that had received either no pretreatment or pretreatment with a contraceptive jelly containing the detergent nonoxynol–9 as spermicide. Transmission was detected by monitoring recipient animals for viral antibodies and by viral cultures of blood leukocytes. Results revealed that a single dose of the infected cell inoculum efficiently transmitted FIV infection when delivered into the vagina or rectum (10 of 11 animals became infected). Pretreatment of the vagina (five animals) or rectum (four animals) with contraceptive jelly protected all animals from transmission by the highly infectious inoculum. The authors conclude that the cat FIV model provides an efficient means for studying transmucosal transmission of lentivirus infections and for assessing vaginal barrier methods that could block transmission. One such barrier method, nonoxynol–9 contraceptive jelly, effectively prevents transmucosal transmission by an FIV–infected cell inoculum.

I.A.i–17
In Vitro Activity of Nonoxynol–9 on HeLa 229 Cells and Primary Monkey Cervical Epithelial Cells Infected With *Chlamydia trachomatis*.

Form: Journal Article.
Author: Patton, D. L.; Wang, S. K.; Kuo, C. C.
Source: Antimicrobial Agents and Chemotherapy. 36(7):1478–82, July 1992.

Published Abstract: Nonoxynol–9 is the active ingredient in a wide variety of vaginal contraceptive preparations. The manufacturer recommendation for optimal contraceptive practice is repeated application every 6 hours. The authors studied the in vitro activity of nonoxynol–9 against *Chlamydia trachomatis* (E/UW–5/Cx) and its toxicity against HeLa 229 cells and monkey cervical epithelial cells. With a contact time of 6 hours, nonoxynol–9 was toxic to HeLa cells at concentrations of 50 µg/ml or greater and to monkey cervical cells at 100 µ/ml or greater. Inhibitory effects of nonoxynol–9 on extracellular *C. trachomatis* were observed at concentrations of 50 µg/ml or greater. Inhibition of intracellular growth of *C. trachomatis* in monkey cervical cells was observed at a nontoxic concentration of 50 µg/ml. The study showed that nonoxynol–9 has antichlamydial activity. However, owing to its toxicity to cervical cells in vitro, the effects of prolonged use of nonoxynol–9 in vivo should be examined further.

I.A.i–18
"PROTECTAID"®: A New Vaginal Sponge With Contraceptive and Antiviral Properties.
Author: Psychovos, A.; Creatsas, G.; Hassan, E.; Georgoulias, V.; Gravanis A.
[See abstract II.C.i.b–9.]

I.A.i–19
Synergistic Effect of Human Leukocyte Interferon and Nonoxynol–9 Against Herpes Simplex Virus Type 2.

Form: Journal Article.
Author: Rapp, F.; Wrzos, H.
Source: Antimicrobial Agents and Chemotherapy. 28(3):449–451, September 1985.

Published Abstract: The nonionic surfactant nonoxynol–9, in combination with human alpha interferon, synergistically reduced the titer of herpes simplex virus type 2 (HSV-2) in vitro. The degree of synergy was highest at an interferon concentration of 10^3 IU/ml and a nonoxynol–9 dilution of 1:1,500. The authors postulate that nonoxynol–9 inactivates

extracellular HSV-2, whereas interferon inhibits HSV-2 replication at the intracellular level.

I.A.i–20
Anti–HIV Screening Technology.

Form: Book Chapter.
Author: Resnick, L.; Busso, M. E.; Duncan, R. C.
Source: IN: Heterosexual Transmission of AIDS Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989. Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M., eds. New York, Wiley–Liss, pp. 311–325, 1990.

Published Abstract: None.
Annotators' Abstract: The performance, development, and evaluation of a fast, quantitative screening assay for determining in vitro the relative efficacy of microbicidal agents in inactivating cell–free human immunodeficiency virus (HIV) are described. Inactivation of viral loads several orders of magnitude greater than that likely to be found in cervical or seminal fluids is desirable. A high–titer virus stock is necessary for these experiments. The spermicide test concentration (1%) was selected so that active agents could be prioritized in comparison with nonoxynol–9. The assay that uses syncytium–formation as a measurement outcome, the microliter plate formats, and the experimental controls is outlined. The compounds evaluated were DP–1, Encare, Semicid, Ortho–Gynol jelly, and Ortho–Creme®.

I.A.i–21
Condoms as Physical and Chemical Barriers Against HIV.

Form: Journal Article.
Author: Rietmeijer, C. A.; Krebs, J. W.; Feorino, P. M.; Judson, F. N.
Source: JAMA. 259(12):1851–53, March 25, 1988.

Published Abstract: In an in vitro model, 20 condoms containing 0.9 ml of 6.6% (vol/vol) nonoxynol–9 and 10 condoms without nonoxynol–9 were tested as physical and chemical barriers against human immunodeficiency virus (HIV). Each condom was mounted on a hollow dildo and placed in a glass cylinder. The HIV inoculum and HIV-free medium were placed on opposite sites of the condom. Intercourse was simulated by pumping the dildo up and down in the cylinder before and after deliberate rupture of the condom. Samples for HIV culture were taken from outside and inside the condom, before and after rupture. After the condoms containing nonoxynol–9 were ruptured, the external concentration of nonoxynol–9 reached 0.25%. No condom without nonoxynol–9 leaked HIV before rupture, but after rupture, HIV could be detected in medium outside of 7 of 10 condoms tested. In none of 20 nonoxynol–9-containing condoms could HIV be detected in the external medium after rupture. Thus, undamaged condoms provide an effective physical barrier against HIV, and nonoxynol–9 may provide an effective chemical barrier as well.

I.A.i–22
Spermicide: Anti–HIV Activity and Cytotoxicity In Vitro.

Form: Journal Article, Letter.
Author: Salole, E. G.; Shepherd, A. J.
Source: AIDS. 7(2):293–295, February 1993.

Published Abstract: None.
Annotators' Abstract: The authors point out that a particular shortcoming in spermicide assessment is the absence of the formulations used for spermicide delivery. The virucidal potencies of nonoxynol–9, other polyoxyethylenes, and chlorhexidine were similar.

I.A.i–23
Spermicide Permeation Through Biocompatible Polymers.

Form: Journal Article.
Author: Saltzman, W. M.; Tena, L. B.
Source: Contraception. 43(5):497–505, May 1991.

Published Abstract: Although spermicides are safe and effective contraceptive and prophylactic agents, they are inconvenient to use. Using a two–chamber diffusion cell, the authors measured the rates of permeation of nonoxynol–9 (N–9), benzalkonium chloride (BK), and chlorhexidine through films of

ethylene–vinyl acetate copolymer (EVAc) and silicone elastomer (Silastic®). Encapsulating N–9, BK, and chlorhexidine into solid polymer matrices, they also measured the rate of spermicide release following immersion in water. In addition, the authors developed equations for predicting the release rate of spermicide from a vaginal ring containing encapsulated spermicide, and tested them using hollow Silastic® rings containing pure N–9 or BK. N–9 diffuses through a thin film of Silastic® several orders of magnitude slower than it does through water. The rates of permeation of N–9 through EVAc, BK through Silastic®, and chlorhexidine through Silastic® were too slow to detect over a 1–week experiment. Polymer matrices of EVAc or Silastic® released N–9 at a controlled rate for several days. Based on these measurements, the authors predict that a vaginal ring containing an inner core of EVAc/N–9, surrounded by a thin, permeable layer of Silastic® will provide a controlled, constant release of N–9 for over 30 days. Because of its low permeability through Silastic®, BK is probably not a good spermicide for a long–acting vaginal ring and, because of its low solubility in water, chlorhexidine is also not a good candidate for controlled release into the vaginal mucus.

I.A.i–24

Survival and Disinfectant Inactivation of the Human Immunodeficiency Virus: A Critical Review.

Form: Journal Article.
Author: Sattar, S. A.; Springthorpe, V. S.
Source: Reviews of Infectious Diseases. 13(3):430–447, May–June 1991.

Published Abstract: The possibility of contracting acquired immunodeficiency syndrome (AIDS) through accidental or inapparent parenteral exposure to human immunodeficiency virus (HIV) has raised concerns among recipients of blood products, health care professionals, and others who have contact either with HIV or with AIDS patients. Along with these concerns has come an increasing interest in the physical and chemical methods that may be used to inactivate HIV in blood products and other contaminated fluids as well as on contaminated objects and surfaces. This review critically examines the available information on the survival of HIV and the methods used to inactivate it, particularly those that rely on chemical disinfection. Although the risk of acquiring HIV from contaminated materials may be slight compared with that of acquiring other blood–borne pathogens, such as hepatitis B virus, the effectiveness of disinfectants used under clinical conditions may have been overestimated.

I.A.i–25

The Effect of Vaginal Lubricants on *Neisseria gonorrhoeae*.

Form: Journal Article
Author: Singh, B.; Cutler, J. C.
Source: American Journal of Obstetrics & Gynecology. 126(3):365–369, October 1, 1976.

Published Abstract: The possible interference of vaginal lubricants in culture diagnosis of gonorrhea was investigated by studying in vitro effects of selected lubricants on *Neisseria gonorrhoeae*. Two lubricants widely used in family planning and other clinics were demonstrated to have a bactericidal effect on *N. gonorrhoeae* when tested with more than one method. Gonococci were killed on contact with Lubrifoam®, even at a 10–percent concentration, and an exposure time as short as 1 minute was sufficient to inhibit the growth on chocolate agar medium. The K–Y® jelly showed less inhibitory effect than Lubrifoam®. These findings suggest that certain vaginal lubricants have bactericidal effects and their presence can inhibit the growth of *Neisseria gonorrhoeae*.

I.A.i–26

Studies on the Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease and Other Genital Infections and Contraception. II. Effect In Vitro of Vaginal Contraceptive and Non–Contraceptive Preparations on *Treponema pallidum* and *Neisseria gonorrhoeae*.
Author: Singh, B.; Cutler, J. C.; Utidjian, H. M.
[See abstract IV.A–28.]

I.A.i–27

Virucidal Effect of Certain Chemical Contraceptives on Type 2 Herpes Viruses.

Form: Journal Article.
Author: Singh, B.; Posti, B.; Cutler, J. C.

Source: American Journal of Obstetrics and Gynecology. 126(4):422–425, October 15, 1976.

Published Abstract: The virucidal effect of several chemical contraceptives was investigated and the findings are reported. The suspension of type 2 herpes simplex virus, containing 10^6 to 10^7 tissue culture infective doses per 0.1 ml, was inactivated on exposure to five different chemical contraceptives. For quantitative estimates of virucidal effect, 10% solutions of these chemical contraceptives were tested with an exposure time of 10 minutes at room temperature. The methods for determination of residual infectivity included virus assays in cultures of Vero cells and human embryo fibroblasts, as well as the intracranial inoculation of mice. Virus infectivity decreased 1,000- to 10,000-fold after contact with chemical contraceptives, indicating a substantial virucidal effect.

I.A.i–28
Correlation Between Hydrophobicity and Resistance to Nonoxynol–9 and Vancomycin for Urogenital Isolates of Lactobacilli.
Author: Tomeczek, L.; Reid, G.; Cuperus, P. L.; McGroarty, J. A.; Van der Mei, H. C.; Bruce, A. W.; Khoury, A. E.; Busscher, H. J.
[See abstract I.F–8.]

I.A.i–29
Evaluation of the Amount of Nonoxynol Available in Condoms for the Inhibition of HIV Using a Method Based on HPLC.

Form: Journal Article.
Author: Trap, R.; Trap, B.; Petersen, C. S.
Source: International Journal of STDs and AIDS. 1(5): 346–348, September 1990.

Published Abstract: A method is described for detection of nonoxynol in condoms, based on methanol–water extraction followed by reverse–phase high–performance liquid chromatography. Using this method, the authors found that approximately 50% of the nonionic surfactant lubricant nonoxynol migrated into elastomers (rubber latex), resulting in a concentration of nonoxynol insufficient to inhibit human immunodeficiency virus (HIV) (less than 0.05%). In order to minimize the risk of sexual transmission of HIV and to ensure spermicidal effect and optimal rubber properties, the concentration of nonoxynol in condoms, therefore, should either be increased, or nonoxynol should be packed separately. Further studies are needed to clarify and determine the solubility and migration of nonoxynols into elastomers.

I.A.i–30
[The Nonoxynol Content in Condoms is Insufficient to Inhibit the Human Immunodeficiency Virus (HIV).] [Danish.]

Form: Journal Article.
Author: Trap, R.; Trap, B.; Petersen, C. S.
Source: Ugeskrift For Laeger. 152(46):3464–66, November 12, 1990.

Published Abstract: The seven types of condoms available in Denmark were examined for nonoxynol content to assess its efficacy in preventing the spread of human immunodeficiency virus (HIV) in conjunction with condom use and possible defects in effectivity (tearing, holes, overflow of semen, sliding off). Compared with the declared content of 40 mg of nonoxynol (100%) per condom, the following nonoxynol quantities could be demonstrated by methanol/water extraction and subsequent high–performance liquid chromatography: one make of condom contained 65%, two 50%–55%, and four 25%–33%. The nonoxynol content was found to be evenly distributed between the outer and inner surface of the condoms. With a theoretical distribution volume of 6 ml (tearing during vaginal coitus), it was found that the three types of condoms examined did not achieve the HIV–inhibiting nonoxynol concentration of 0.05% when the quantity of nonoxynol was measured on the distal 5 cm of the condoms. In anal sex, the distribution volume is greater, resulting in lower nonoxynol concentrations and, therefore, increased risk for HIV infection. It is concluded that the nonoxynol content in condoms marketed in Denmark should be increased in order to inactivate HIV in the event of condom failure.

I.A.i–31
Nonoxynol–9 and HTLV III.

Form: Journal Article, Letter.
Author: Voeller, B.
Source: Lancet. 1(8490):1153, May 17, 1986.

Published Abstract: None.
Annotators' Abstract: Nonoxynol–9 (5%) inactivates human T–lymphotropic virus III/lymphadenopathy–associated virus (HTLV–III/LAV) very rapidly (<60 seconds) in vitro. A 5% concentration of nonoxynol–9 destroys lymphocytes.

Commentary: HTLV–III/LAV is now called HIV–1.

I.A.i–32
Mineral Oil Lubricant Causes Rapid Deterioration of Latex Condom.

Form: Journal Article.
Author: Voeller, B.; Coulson, A. H.; Bernstein, G. S.; Nakamura, R. M.
Source: Contraception. 39(1):95–102, 1989.

Published Abstract: As little as 60 seconds exposure of commercial latex condoms to mineral oil, a common component of hand lotions and other lubricants used during sexual intercourse, caused an approximately 90% decrease in the strength of the condoms, as measured by their burst volumes in the International Standards Organization (ISO) Air Burst Test. Burst pressures were also reduced, although less dramatically. Lubricants such as Vaseline Intensive Care Lotion® and Johnson's Baby Oil®, each containing mineral oil, were shown to affect condom integrity. Five minutes exposure of condoms to glycerol, a frequent component of hand lotions and "personal lubricants" did not significantly affect burst volume or pressure. Aqueous nonoxynol–9 spermicide did not affect either burst index. The implications of these results for contraception and protection from sexually transmitted diseases, including AIDS, are discussed.

I.A.i–33
High–Performance Liquid Chromatographic (HPLC) Analysis of Oligomeric Components of the Spermicide Nonoxynol–9.

Form: Journal Article.
Author: Walter, B. A.; Digenis, G. A.
Source: Pharmaceutical Research. 8(3):409–411, March 1991.

Published Abstract: The commercially available nonoxynol–9 spermicide is a multicomponent mixture of oligomers. When nonoxynol–9 was separated by normal phase gradient high–performance liquid chromatography (HPLC), 17 components were shown to exist in the commercial mixture. These oligomeric components follow a Poisson distribution around the most abundant oligomer, EO 8 (11.7%). Select oligomers were isolated by preparative HPLC (Rt = 19.6, 34.0, 45.6, 51.2, 61.6, and 79.2 min) and purified by HPLC. These were identified by fast atom bombardment mass spectrometry (FAB–MS) and nuclear magnetic resonance (NMR) to be the oligomers EO 3, EO 6, EO 8, EO 9, EO 11, and EO 16, respectively.

I.A.i–34
Nonoxynol–9 Protects Mice Against Vaginal Transmission of Genital Herpes Infections.

Form: Journal Article.
Author: Whaley, K. J.; Barratt, R. A.; Zeitlin, L.; Hoen, T. E.; Cone, R. A.
Source: Journal of Infectious Diseases. 168(4):1009–11, October 1993.

Published Abstract: A vaginal application of a commercially available contraceptive jelly containing nonoxynol–9 prevented vaginal transmission of herpes simplex virus type 2 (HSV–2) infection in the mouse. When nonoxynol–9 jelly was delivered to the vagina with the virus inoculum, 20 seconds before inoculum or 5 minutes before inoculum, mice were completely protected from visible infection ($P < 0.001$). Protection lasted for at least 30 minutes ($P < 0.03$), and significant protection occurred even when the nonoxynol–9 jelly was delivered 15 minutes after the HSV–2 inoculum ($P < 0.05$). These results are consistent with results of studies using nonoxynol–9 products in other animal models and suggest that nonoxynol–9–based contraceptive products can provide significant protection against vaginal transmission of enveloped virus infections in animals.

I.A.*ii*. Preclinical Studies of Detergent Microbicides–Benzalkonium Chloride.

I.A.ii–1
Inactivation of Herpes Simplex Viruses by Nonionic Surfactants.
Author: Asculai, S. S.; Weis, M. T.; Rancourt, M. W.; Kupferberg, A. B.
[See abstract I.A.i–1.]

I.A.ii–2
New and Existing Spermicides With Virucidal Properties.
Author: Chantler, E. N.
[See abstract IV.A–7.]

I.A.ii–3
HIV Inactivation by a Spermicide Containing Benzalkonium Chloride.

Form: Journal Article.
Author: Chermann, J. C.; Barre–Sinoussi, F.; Henin, Y.; Marechal, V.
Source: AIDS–Forschung. 2(2):85–86, 1987.

Published Abstract: No virus production was observed in cultures of peripheral blood lymphocytes infected with human immunodeficiency virus (HIV) (105 counts per minute per milliliter reverse transcriptase activity) that had been treated with benzalkonium chloride (0.012% for 10 to 15 minutes).

I.A.ii–4
[Benzalkonium in Local Contraception and Sexually Transmitted Diseases.] [Italian.]
Author: Frateschi, M.; Zandonini, G. F.; Mazzoleni, G. C.
[See abstract II.C.i.b–4.]

I.A.ii–5
The Susceptibility of Organisms Associated With Bacterial Vaginosis to Spermicidal Compounds, In Vitro.
Author: Jones, B. M.; Willcox, L. M.
[See abstract I.A.i–10.]

I.A.ii–6
Bovine Beta-Lactoglobulin Modified by 3-Hydroxyphthalic Anhydride Blocks the CD4 Cell Receptor for HIV.

Form: Journal Article.
Author: Neurath, A. R.; Jiang, S.; Strick, N.; Lin, K.; Li, Y. Y.; Debnath, A. K.
Source: Nature Medicine. 2(2):230–234, February 1996.

Published Abstract: Sexual transmission is the most frequent (86%) route of adult human immunodeficiency virus type 1 (HIV-1) transmission worldwide. In the absence of a prophylactic anti-HIV vaccine, other methods of preventing infection should be implemented. Virucidal spermicides have been considered for this purpose, but their application is contraindicated by adverse effects. Anti-HIV drugs or virus-neutralizing monoclonal antibodies are expensive, suggesting that their wide use in topical chemoprophylaxis is unlikely. This emphasizes the importance of developing other methods for preventing HIV transmission. The target cells for sexual and mucosal HIV transmission include T lymphocytes, monocytes and macrophages, and dendritic cells. Therefore, compounds blocking HIV-CD4 binding are expected to inhibit virus transmission. In exploring the possibility that chemical modification of food proteins might lead to compounds with anti-HIV-1 activity, we found that bovine beta-lactoglobulin (beta-LG), modified by 3-hydroxyphthalic anhydride (3HP-beta-LG), (1) blocked at nanomolar concentrations the binding to CD4 of HIV and simian immunodeficiency virus (SIV) surface glycoproteins and monoclonal antibodies specific for the HIV binding site on CD4 and (2) inhibited infection by HIV-1, including primary virus isolates, by HIV-2 and SIV. The inexpensive and widely available source (whey) for production of 3HP-beta-LG suggests its potential application (nonparenteral) for diminishing the frequency of HIV transmission.

I.A.ii–7
"PROTECTAID"®: A New Vaginal Sponge With Contraceptive and Antiviral Properties.
Author: Psychovos, A.; Creatsas, G.; Hassan, E.; Georgoulias, V.; Gravanis A.
[See abstract II.C.i.b–9.]

I.A.ii–8
Spermicide Permeation Through Biocompatible Polymers.
Author: Saltzman, W. M.; Tena, L. B.
[See abstract I.A.i–23.]

I.A.ii–9
Inactivation of Human Immunodeficiency Virus Type 1 in Tissue Culture Fluid and in Genital Secretions by the Spermicide Benzalkonium Chloride.

Form: Journal Article.
Author: Wainberg, M. A.; Spira, B.; Bleau, G.; Thomas, R.
Source: Journal of Clinical Microbiology. 28(1):156–158, January 1990.

Published Abstract: The authors have shown that the spermicidal agent benzalkonium chloride can exert a direct inhibitory effect on the viral reverse transcriptase activity of human immunodeficiency virus type 1 (HIV–1) when utilized at concentrations of 0.05% and higher. Benzalkonium chloride was tested on 10 samples of HIV derived from H–9 cells, as well as on the seminal secretions of four male HIV–positive patients and the vaginal secretions of four female patients. Exposure of HIV–1 to benzalkonium chloride at concentrations of more than 0.05% completely destroyed viral infectivity, as assessed on susceptible target cells. The authors have further shown that HIV–1, which is present in both seminal and genital secretions, can be inactivated in such fluids by direct exposure to benzalkonium chloride.

I.A.*iii.* Preclinical Studies of Detergent Microbicides–Chlorhexidine.

I.A.iii–1
New and Existing Spermicides With Virucidal Properties.
Author: Chantler, E. N.
[See abstract IV.A–7.]

I.A.iii–2
Inactivation of Human Immunodeficiency Virus by Betadine® Products and Chlorhexidine.
Author: Harbison, M. A.; Hammer S. M.
[See abstract I.D–2.]

I.A.iii–3
Spermicide: Anti–HIV Activity and Cytotoxicity In Vitro.
Author: Salole, E. G.; Shepherd, A. J.
[See abstract I.A.i–22.]

I.A.iii–4
Spermicide Permeation Through Biocompatible Polymers.
Author: Saltzman, W. M.; Tena, L. B.
[See abstract I.A.i–23.]

I.A.*iv.* Preclinical Studies of Detergent Microbicides–Menfegol.

I.A.iv–1
Anti–HIV Screening Technology.
Author: Resnick, L.; Busso, M. E.; Duncan, R. C.
[See abstract I.A.i–20.]

I.A.iv–2
In Vitro Effect of Menfegol on *Neisseria gonorrhoeae*.

Form: Journal Article.
Author: Yamai, S.; Kuroki, T.; Watanabe, Y.; Takizawa, K.
Source: Kansenshogaku Zasshi. 63(10):1178–81, October 1989.

Published Abstract: The bacteriostatic and bactericidal effects of menfegol, which has been used as a spermicide on *Neisseria gonorrhoeae*, were investigated in vitro. The minimum inhibitory concentrations (MICs) of *N. gonorrhoeae* to menfegol fell into two groups. Resistant strains showed MICs of >3,200 µg/ml, while the MICs of sensitive strains were #200 µg/ml. When the resistant strains were suspended in several concentrations of menfegol and incubated at 35EC, no concentrations inactivated the gonococci completely. However, the number of organisms decreased remarkably within 30 minutes.

I.A.*v.* Preclinical Studies of Detergent Microbicides–Octoxynol.

I.A.v–1
The Susceptibility of Organisms Associated With Bacterial Vaginosis to Spermicidal Compounds, In Vitro.
Author: Jones, B. M.; Willcox, L. M.
[See abstract I.A.i–10.]

I.A.v–2
Spermicide: Anti–HIV Activity and Cytotoxicity In Vitro.
Author: Salole, E. G.; Shepherd, A. J.
[See abstract I.A.i–22.]

I.A.*vi.* Preclinical Studies of Detergent Microbicides–Other.

I.A.vi.–1
"PROTECTAID"®: A New Vaginal Sponge With Contraceptive and Antiviral Properties.
Author: Psychovos, A.; Creatsas, G.; Hassan, E.; Georgoulias, V.; Gravanis A.
[See abstract II.C.i.b–9.]

I.B.*i.* Preclinical Studies of Polypeptide Microbicides–Gramicidin.

I.B.i–1
Anti–HIV Effect of Gramicidin In Vitro: Potential for Spermicide Use.

Form: Journal Article.
Author: Bourinbaiar, A. S.; Krasinski, K.; Borkowsky, W.
Source: Life Sciences. 54(1):PL5–9, 1994.

Authors' Abstract: Gramicidin, a cation channel–forming ionophore with antibacterial properties, was studied in vitro for inhibition of human immunodeficiency virus (HIV) infection of MT–4 lymphocytes. Effective antiviral concentrations required for complete HIV inactivation were three orders of magnitude lower than 10 micrograms/ml cytotoxic dose. Gramicidin, routinely used as a contraceptive agent, should be considered for clinical application as a spermicide with antiviral activity.

I.B.i–2
Comparative In Vitro Study of Contraceptive Agents With Anti–HIV Activity: Gramicidin, Nonoxynol–9, and Gossypol.
Author: Bourinbaiar, A. S.; Lee–Huang, S.
[See abstract I.A.i–3.]

I.B.i–3
The Effect of Gramicidin, Microbicide and Spermicide, Against HIV and Herpes Virus Infections.

Form: Journal Article.
Author: Bourinbaiar, A. S.; Fruhstorfer, E. C.; Lopes, R. Metatron, Inc., 31 Stuyvesant Street, New York, NY 10003, U.S.A.
Source: We.A.513, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: Currently available spermicides with anti-HIV activity, such as nonoxynol-9, are not effective. Since 80% of AIDS cases are sex-borne, better alternative substances are urgently needed. *Methods*: The serial ten-fold dilutions of gramicidin were tested in vitro for the suppression of HIV and herpes simplex viruses type 1 and 2 (HSV) infections using standard antiviral assays specific for each type of virus. Various spermicidal agents, e.g., nonoxynol-9, gossypol and antiviral agents, e.g., acyclovir, dextran sulfate, were used as controls. *Results*: Gramicidin inhibited both HIV and HSV infection at doses that were not cytotoxic. Based on several experiments with multiple replicates for each dilution of drug it appears that 100% inhibition of HIV and HSV infections was achieved by 10 ng and 100 ng of gramicidin respectively. In contrast, control antivirals and spermicides were either less efficient, requiring much larger doses, or too toxic. Gramicidin was also effective against acyclovir-resistant strains of HSV. *Conclusions*: Extensive clinical trials were carried out in the former Soviet Union to identify the spermicidal activity of gramicidin. As a result, gramicidin has been routinely used by millions of individuals. Gramicidin is a safe and inexpensive antibiotic approved by FDA for topical use. In the U.S.A. gramicidin is used in topical opthalmic preparations (Neosporin) at concentration of less than 25 µg/ml rarely causing irritation as it is poorly absorbed by the skin or mucous membranes. Due to its activity against fungal (C. Albicans) and protozoan infections gramicidin is useful against STDs. This compound has a good potential as a spermicidal/microbicide with anti-HIV and anti-HSV activities for the following reasons: it is cheap, stable, non-irritating, does not smell or stain, and 1000-times more potent than nonoxynol-9.

I.B.*ii.* Preclinical Studies of Polypeptide Microbicides–Other.

I.C.*i.* Preclinical Studies of Polysaccharide Microbicides–Carrageenan.

I.C.i–1
A New Procedure for the Isolation of Anti–HIV Compounds (Polysaccharides and Polyphenols) From the Marine Alga *Fucus vesiculosis*.

Form: Journal Article.
Author: Beress, A.; Wassermann, O.; Bruhn, T.; Beress, L.; Kraiselburd, E. N.; Gonzalez, L. V.; de Motta, G. E.; Chavez, P. I.
Source: Journal of Natural Products. 56(4):478–488, April 1993.

Authors' Abstract: Anti–HIV–active polysaccharides and polyphenols were isolated from the brown seaweed *Fucus vesiculosis* by hot H_2O extraction of both the intact and the homogenized algae. This was followed by XAD2 chromatography and by sequential precipitation of the non–absorbed compounds with glacial HOAc and thereafter EtOH. The precipitate was solubilized, dialyzed against distilled H_2O, and chromatographed on SP–Sephadex C25 and on QAE–Sephadex A25. This was followed by gel filtration on Sephadex G50 and Sephadex G100 and finally by HPLC on a Shodex Ionpak S–804 column. For comparison, the commercial product fucoidan, a sulfated algal polysaccharide, was also further purified by the chromatographic techniques mentioned above. The isolated freeze–dried fractions obtained by these procedures were tested for inhibition of both HIV–induced syncytium formation and HIV reverse transcriptase enzyme activity. Some of these fractions inhibited both of these activities at concentrations that were not cytotoxic.

I.C.i–2
Maleylated–Human Serum Albumin Inhibits HIV–1 Infection In Vitro.
Author: Takami, M.; Sone, T.; Mizumoto, K.; Kino, K.; Tsunoo, H.
[See abstract I.H–14.]

I.C.*ii*. Preclinical Studies of Polysaccharide Microbicides–Heparin Sulfate.

I.C.ii–1
Novel Sulfated Polysaccharides: Dissociation of Anti–Human Immunodeficiency Virus Activity From Antithrombin Activity.
Author: Baba, M.; De Clercq, E.; Schols, D.; Pauwels, R.; Snoeck, R.; Van Boeckel, C.; Van Dedem, G.; Kraaijeveld, N.; Hobbelen, P.; Ottenheijm, H.; et al.
[See abstract I.C.v–1.]

I.C.ii–2
Anti–Human Immunodeficiency Virus Type 1 Activity of Sulfated Monosaccharides: Comparison With Sulfated Polysaccharides and Other Polyions.
Author: Bagasra, O.; Whittle, P.; Heins, B.; Pomerantz, R. J.
[See abstract I.C.v–3.]

I.C.ii–3
The V3 Region of the Envelope Glycoprotein of Human Immunodeficiency Virus Type 1 Binds Sulfated Polysaccharides and CD4–Derived Synthetic Peptides.
Author: Batinic, D.; Robey, F. A.
[See abstract I.C.v–4.]

I.C.ii–4
Anti–HIV Type 1 Properties of Chemically Modified Heparins With Diminished Anticoagulant Activity.

Form: Journal Article.
Author: Lopalco, L.; Ciccomascolo, F.; Lanza, P.; Zoppetti, G.; Caramazza, I.; Leoni, F.; Beretta, A.; Siccardi, A. G.
Source: AIDS Research and Human Retroviruses. 10(7):787–793, July 1994.

Published Abstract: Several groups have reported that sulfated polysaccharides are potent and selective in vitro inhibitors of human immunodeficiency virus type 1 (HIV–1); however, their therapeutic application is limited by their anticoagulant activity. In view of possible improvements in therapeutic potential, a number of heparin derivatives with reduced anticoagulant activity were studied for their inhibitory activity in an HIV–dependent syncytium formation assay and were compared with standard anionic polysaccharides such as sodium heparin, dextran sulfate, and heparin sulfate. The chemical modifications introduced in the heparin molecule included succinylation of desulfated N groups (Suc–H), exhaustive periodate oxidation and reduction (RO–H), and controlled nitrous acid degradation (LMW–H). The most pronounced anti–HIV activity was observed with RO–H, Suc30–H (standard heparin, 30% succinylated), and Suc100–LMW–H (low molecular weight heparin, 100% succinylated); the latter retained only 5% of the anticoagulant activity of standard heparin, whereas RO–H and Suc30–H retained approximately 35% of the anticoagulant activity of standard heparin. A safety ratio (arbitrary units of anti–HIV activity per anticoagulant international unit) was calculated. By this parameter, RO–H, Suc30–H, and Suc100–LMW–H were, respectively, 48–, 3.6–, and 1,644–fold safer than standard heparin.

I.C.*iii.* Preclinical Studies of Polysaccharide Microbicides–Dextran Sulfate.

I.C.iii–1
Anti–Angiogenesis Agent DS–4152 is a Potent and Selective Inhibitor of HIV–1 Replication In Vitro.

Form: Journal Article.
Author: Baba, M.; Shigeta, S.; Ikeuchi, T.; Korenaga, H.; Osada, Y.
Source: AIDS. 8(1):43–48, January 1994.

Published Abstract: Objective: The authors conducted a study to determine whether the anti–angiogenesis agent DS–4152 inhibits the replication of human immunodeficiency virus type 1 (HIV–1) in vitro. Design: A sulfated polysaccharide–peptidoglycan, DS–4152, has recently been identified as a potent and selective inhibitor of Kaposi's sarcoma; therefore, the authors feel that an evaluation of the anti–HIV–1 activity of DS–4152 alone and in combination with dideoxynucleosides is in order. Activity of DS–4152 against HIV–1 replication was examined in MT–4, MOLT–4, and peripheral blood lymphocyte cells. The inhibitory effect of the compound on syncytium formation was determined by cocultivation of MOLT–4 cells with MOLT–4/IIIB cells. Inhibition of virus adsorption to the host cells was measured by a p24 antigen capture enzyme–linked immunosorbent assay. Results: DS–4152 showed potent and selective inhibition of HIV–1 replication in the cell systems. Its 50% effective concentration for HIV–1 (IIIB strain) in MT–4 cells was 0.7 µg/ml. The compound was not cytotoxic at concentrations of #100 µg/ml. DS–4152 proved inhibitory to syncytium formation and virus adsorption. The anti–HIV–1 activities of zidovudine, dideoxycytidine, and dideoxyinosine were not affected by the presence of DS–4152. Conclusion: DS–4152 has the potential to function as an anti–HIV–1 as well as an anti–angiogenesis agent. In order to determine this possibility, consequences of DS–4152 infusion on HIV–1 p24 serum levels and CD4+ cell counts are being examined in ongoing clinical trials in the United States on patients with Kaposi's sarcoma secondary to acquired immunodeficiency syndrome.

I.C.iii–2
Activity of Dextran Sulfate and Other Polyanionic Polysaccharides Against Human Immunodeficiency Virus.

Form: Journal Article.
Author: Bagasra, O.; Lischner, H. W.
Source: Journal of Infectious Diseases. 158(5):1084–87, November 1988.

Published Abstract: None.
Annotators' Abstract: Studies have demonstrated that dextran sulfate blocks the formation of syncytia between human immunodeficiency virus (HIV)–producing cells and CD–4–bearing target cells. This paper describes the in vitro effect of dextran sulfate (various molecular weights) and three other sulfated polysaccharides on the inhibition of HIV syncytium formation and HIV replication. The authors also correlated the inhibitory effect and the anticoagulant effect of dextran sulfate and sulfated polysaccharides on HIV. They conclude that dextran sulfate and other polyanionic agents prevent HIV syncytium formation in cultured cells in addition to blocking virus replication. Although the mechanism was not determined, it does not seem to be surface modification of the target cell. Dextran sulfate seems to have affinity for gp120 and gp41 of the HIV envelope. The effect of dextran sulfate on reverse transcriptase was not determined, nor was its applicability to the in vivo cell–to–cell spread of HIV.

I.C.iii–3
Anti–Human Immunodeficiency Virus Type 1 Activity of Sulfated Monosaccharides: Comparison With Sulfated Polysaccharides and Other Polyions.
Author: Bagasra, O.; Whittle, P.; Heins, B.; Pomerantz, R. J.
[See abstract I.C.v–3.]

I.C.iii–4
The V3 Region of the Envelope Glycoprotein of Human Immunodeficiency Virus Type 1 Binds Sulfated Polysaccharides and CD4–Derived Synthetic Peptides.
Author: Batinic, D.; Robey, F. A.
[See abstract I.C.v–4.]

I.C.iii–5

Dextran Sulfate Blocks Antibody Binding to the Principal Neutralizing Domain of Human Immunodeficiency Virus Type 1 Without Interfering With gp120–CD4 Interactions.

Form: Journal Article.
Author: Callahan, L. N.; Phelan, M.; Mallinson, M.; Norcross, M. A.
Source: Journal of Virology. 65(3):1543–50, March 1991.

Published Abstract: The mechanism of the antiviral activity of sulfated polysaccharides on human immunodeficiency virus type 1 (HIV–1) was investigated by determining the effect of dextran sulfate on the binding of CD4 and several anti–gp120 monoclonal antibodies to both recombinant and cell surface gp120. Dextran sulfate did not interfere with the binding of sCD4 to rgp120 on enzyme–linked immunosorbent assay (ELISA) plates or in solution, and did not block sCD4 binding to cells infected with HIV–1 or cells expressing gp120 on the cell surface. Dextran sulfate had minimal effects on rgp120 binding to CD4+ cells at concentrations that effectively prevent HIV replication. In contrast, it potently inhibited the binding of both rgp120 and cell surface gp120 to several monoclonal antibodies directed against the principal neutralizing domain of gp120 (V3). In an ELISA format, dextran sulfate enhanced the binding of monoclonal antibodies to amino–terminal regions of gp120 and had no effect on antibodies directed to other regions of gp120, including the carboxy terminus. The inhibitory effects of polyanionic polysaccharides on viral binding, viral replication, and formation of syncytia therefore appear mediated by interactions with positively charged amino acids concentrated in the V3 region. This high local positive charge density, unique to the V3 loop, leads us to propose that this property is critical to the function of the V3 region in mediating envelope binding and subsequent fusion between viral and cell membranes. The specific interaction of dextran sulfate with this domain suggests that structurally related molecules on the cell surface, such as heparan sulfate, may be additional targets for HIV binding and infection.

I.C.iii–6
Pharmacokinetic Analysis of Dextran Sulfate in Rats as it Pertains to Clinical Usefulness for Therapy of HIV Infection.

Form: Journal Article.
Author: Hartman, N. R.; Johns, D. G.; Mitsuya, H.
Source: AIDS Research and Human Retroviruses. 6(6):805–812, June 1990.

Published Abstract: The authors administered radiolabeled dextran sulfate (DS) (^{3}H–labeled on the reducing end, molecular weight approximately 8,000) to rats. High–performance liquid chromatography (HPLC) analysis of plasma from animals that were given [^{3}H]DS intravenously revealed an initial plasma half–life of about 30 minutes. Of the [^{3}H]DS administered, 11% was recovered in the urine in 24 hours; this material represented minor breakdown, with a molecular weight of 4,000 as determined by size–exclusion HPLC analysis. When administered orally, the apparent bioavailability of [^{3}H]DS was 6.8%, based on the recovered radioactivity; however, the molecular weight of the radioactive material obtained from the plasma was all <200, indicating that no detectable intact DS was absorbed upon oral administration. Only 2% of orally administered [^{3}H]DS was found in the 24–hour urine; this material also had a molecular weight of <200. With a molecular weight of <2,300, [^{3}H]DS had no effect against human immunodeficiency virus (HIV); in the presence of higher concentrations of human serum, more DS was required for antiviral effect. Although the pharmacokinetics of DS in rats can differ from that of humans to some extent, these data suggest that oral administration of DS is unlikely to produce significant antiretroviral effect against HIV in vivo and that higher plasma levels of DS may be necessary than those inferred from earlier in vitro data.

I.C.iii–7
Dextran Sulphate Reduces Diphenylhexatriene Anisotropy in Human Peripheral Blood Lymphocytes Impact on Plasma Membrane Fluidity and HIV–Cytopathogenicity.

Form: Journal Article.
Author: Lehr, H. A.; Zimmer, J. P.; Hubner, C.; Reisinger, E. C.; Kohlschutter, A.; Schmitz, H.
Source: Journal of Antimicrobial Chemotherapy. 28(5):677–680, November 1991.

Published Abstract: The cytopathogenicity of

HIV and other enveloped viruses is reduced by membrane fluidizing agents and by dextran sulphate (DS). To investigate whether DS exerts its antiviral action via plasma membrane fluidization of host cells, we performed anisotropy measurements on human peripheral blood lymphocytes using the fluorescent marker diphenylhexatriene. Anisotropy was decreased in DS–exposed peripheral blood lymphocytes, indicating increased fluidity in the hydrophobic membrane interior.

I.C.iii–8
Anti–HIV Type 1 Properties of Chemically Modified Heparins With Diminished Anticoagulant Activity.
Author: Lopalco, L.; Ciccomascolo, F.; Lanza, P.; Zoppetti, G.; Caramazza, I.; Leoni, F.; Beretta, A.; Siccardi, A. G.
[See abstract I.C.ii–4.]

I.C.iii–9
Molecular Interaction Between HIV–1 Major Envelope Glycoprotein and Dextran Sulfate.

Form: Journal Article.
Author: Mbemba, E.; Chams, V.; Gluckman, J. C.; Klatzmann, D.; Gattegno, L.
Source: Biochimica et Biophysica Acta. 1138(1):62–67, January 16, 1992.

Published Abstract: The authors investigated the molecular–level interaction between human immunodeficiency virus type 1 (HIV–1) recombinant gp160 (rgp160) and low–molecular–weight dextran sulfate. They demonstrated the occurrence of a specific interaction between rgp160 and sulfated dextran beads that is saturable, pH–dependent, and inhibitable by soluble dextran sulfate but not by soluble dextran. This specific interaction has a low affinity, with an estimated diffusion constant (K_d) in the range of 10^4 M. In addition, the binding of rgp160 to soluble recombinant CD4 (sT4) can only be inhibited by the preincubation of rgp160, but not of sT4, with dextran sulfate. Taken together, these results demonstrate the occurrence of a low–affinity but specific interaction between dextran sulfate and rgp160. This may account, at least in part, for the anti–HIV–1 activity of dextran sulfate.

I.C.iii–10
Investigations Into the Mechanism by Which Sulfated Polysaccharides Inhibit HIV Infection In Vitro.
Author: McClure, M. O.; Moore, J. P.; Blanc, D. F.; Scotting, P.; Cook, G. M.; Keynes, R. J.; Weber, J. N.; Davies, D.; Weiss, R. A.
[See abstract I.C.v–7.]

I.C.iii–11
CD4–Derived Peptide and Sulfated Polysaccharides Have Similar Mechanisms of Anti–HIV Activity Based on Electrostatic Interactions With Positively Charged gp120 Fragments.

Form: Journal Article.
Author: Meshcheryakova, D.; Andreev, S.; Tarasova, S.; Sidorova, M.; Vafina, M.; Kornilaeva, G.; Karamov, E.; Khaitov, R.
Source: Molecular Immunology. 30(11):993–1001, August 1993.

Authors' Abstract: The mechanism of antiviral activity of the CD4–derived peptide 75–99 was compared with that of sulfated polysaccharides. A set of peptides representing all the high positive charge density regions of gp120 and gp41 was used to determine whether electrostatic interactions occur between these negatively charged agents and positively charged HIV envelope fragments. Synthetic peptide AZ2, amino acids 75–99 from V1 CD4, KIEDSDTYIC(Acm)–EVEDQKEEVQLLVFG, and dextran sulfate 500,000 (DS 500) were used as inhibitory agents of antibody binding in ELISA using: (1) anti–peptide rabbit antibodies; (2) sera from HIV infected persons. Peptide AZ2 and DS were both shown to block antibody binding to peptide (301–323) from the principal neutralizing domain (PND) and peptide (495–516) from the gp120 C–terminus. The blocking concentrations were 1–2 micrograms/ml for DS and 125–250 micrograms/ml for AZ2. The ELISA system based on rabbit anti–peptide antibodies was less sensitive than that based on positive human sera. Chemical modification of lysine epsilon–amino groups of these peptides resulted in complete failure to bind with either DS or AZ2. A correlation was found between the inhibitory activities of a number of sulfated polysaccharides in a syncytium formation assay and in peptide ELISA. The mechanism of direct interactions of specific regions of gp120 with the CDR3–like region of CD4 is proposed.

I.C.iii–12

Influence of Host Cell Type and V3 Loop of the Surface Glycoprotein on Susceptibility of Human Immunodeficiency Virus Type 1 to Polyanion Compounds.

Form: Journal Article.
Author: Meylan, P. R.; Kornbluth, R. S.; Zbinden, I.; Richman, D. D.
Source: Antimicrobial Agents and Chemotherapy. 38(12):2910–16, December 1994.

Published Abstract: Dextran sulfate is a potent inhibitor of human immunodeficiency virus (HIV) binding and of replication in lymphocytic cell lines. In this study, the authors demonstrate that the effect of dextran sulfate and heparin depends on the host cell type and on the V3 loop, the principal neutralizing determinant of HIV gp120. In particular, when dextran sulfate was tested on primary human macrophages infected with macrophage–tropic viruses, enhancement of infection was observed in 6 of 11 independent macrophage preparations and with 5 of 13 primary HIV isolates. The authors conclude that their in vitro observations might explain why enhanced HIV replication was observed in HIV–infected patients treated with dextran sulfate.

I.C.iii–13

Differential Inhibition of HIV–1 Cell Binding and HIV–1–Induced Syncytium Formation by Low Molecular Weight Sulphated Polysaccharides.

Form: Journal Article.
Author: Montefiori, D. C.; Robinson, W. E.; Modliszewski, A.; Rowland, J. M.; Schuffman, S. S.; Mitchell, W. M.
Source: Journal of Antimicrobial Chemotherapy. 25(3):313–318, March 1990.

Published Abstract: Dextran sulfate (molecular weight (MW) 5,000 and 8,000) and a polysulfated glycosaminoglycan (MW 10,000), at concentrations that provided complete protection in a homologous infection assay, failed to block syncytium formation and the resulting cytopathic effect when MT–2 cells were mixed with H9/human immunodeficiency virus type 1 (HIV–1) cells. These substances also had no antiviral activity when added to virally challenged cells at a time when binding and entry were complete. However, a high molecular weight (500,000) dextran sulfate blocked HIV–1 infection at both stages. Thus, the gp120–CD4 interactions mediating HIV–1 binding and HIV–1–induced syncytium formation are differentially affected by this class of polyanionic substances. Furthermore, size may be a determining factor in their potential application as an anti–HIV treatment.

I.C.iii–14

Anti–HIV Activity of Dextran Sulphate as Determined Under Different Experimental Conditions.

Form: Journal Article.
Author: Nakashima, H.; Yoshida, O.; Baba, M.; De Clercq, E.; Yamamoto, N.
Source: Antiviral Research. 11(5–6):233–246, June–July 1989.

Published Abstract: Dextran sulfate is a potent and selective inhibitor of human immunodeficiency virus type 1 (HIV–1). Its anti–HIV–1 activity has been investigated under varying experimental conditions. MT–4 cells were infected with HIV–1 at different multiplicities of infection (MOI), and were treated with either dextran sulfate, 3'–azido–2',3'–dideoxythymidine (AZT), or anti–HIV–1 serum obtained from an AIDS–related complex (ARC) patient. Dextran sulfate suppressed HIV–1 replication (as monitored by viral antigen expression) when the MOI was 0.01 or 0.1. It was ineffective at an MOI of 1.0. The anti–HIV–1 serum was only partially effective at an MOI of 0.01 and ineffective at an MOI of 0.1 or 1.0. AZT proved effective at all three MOIs. Cocultures of uninfected and HIV–1–infected MT–4 cells were protected against destruction by dextran sulfate at a concentration of 10 and 100Fg/ml. To suppress viral antigen expression fully, a concentration of 100 Fg/ml was needed. When used at this concentration, a 1–hour contact of dextran sulfate with the cells during the virus adsorption period sufficed to suppress HIV–1 antigen expression. In this sense, dextran sulfate behaved like the anti–HIV–1 serum. Dextran sulfate also behaved like OKT–4A in that they both inhibited HIV–1 attachment to the MT–4 cells, whereas OKT–4 failed to do so. However, dextran sulfate did not affect the binding of OKT–4A to the cells. The present results support the concept that the main

anti–HIV–1 activity of dextran sulfate is inhibiting the virus from binding to its target cells, a function highly dependent on its sulfate content.

I.C.iii–15

Effect of Polyanionic Compounds on Intracutaneous and Intravaginal Herpes Virus Infection in Mice: Impact on the Search for Vaginal Microbicides With Anti-HIV Activity.

Form: Journal Article.
Author: Neyts, J.; De Clercq, E.
Source: Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology. 10(1):8–12, September 1, 1995.

Published Abstract: Several polyanionic compounds were found to suppress intracutaneous infection of hairless mice with herpes simplex virus type 2 (HSV-2) only when present at the time of inoculation. Because (1) sexual intercourse is a major route of infection with human immunodeficiency virus (HIV); (2) due to the species-specificity of HIV, there is no small animal model to study intra-vaginal HIV infection; (3) HIV is equally or even more sensitive than HSV-2 to several polyanions; and (4) sulfated polymers may prevent the adhesion of (HIV-infected) lymphocytes to epithelial cells, we evaluated the effect the compounds on intravaginal infection of mice with HSV-2. To this end, mice were infected intravaginally with a virus-compound mixture. Under the conditions used, the polysulfate dextran sulfate conferred only partial protection against infection and virus-induced mortality. However, PAVAS (a co-polymer of acrylic acid with vinylalcohol sulfate) completely protected against the infection. These results should be taken into account when planning clinical studies with a vaginal polysulfate formulation for the prevention of sexually transmitted HIV and/or HSV-2 infections.

I.C.*iv.* Preclinical Studies of Polysaccharide Microbicides–Curdlan Sulfate.

I.C.iv–1
Mechanism of the Inhibitory Effect of Curdlan Sulfate on HIV–1 Infection In Vitro.

Form: Journal Article.
Author: Jagodzinski, P. P.; Wiaderkiewicz, R.; Kurzawski, G.; Kloczewiak, M.; Nakashima, H.; Hyjek, E.; Yamamoto, N.; Uryu, T.; Kaneko, Y.; Posner, M. R.; et al.
Source: Virology. 202(2):735–745, August 1, 1994.

Published Abstract: To study the mechanism by which sulfated polysaccharides with 1,3–beta–d–glucan as a main chain exert activity against human immunodeficiency virus type 1 (HIV–1), the authors analyzed the effects of curdlan sulfate (CRDS) on HIV–1 infection of SupT–1 cells and peripheral blood mononuclear cells. CRDS had no effect on virions, weakly inhibited HIV–1 attachment to cells, and had to be present for 24 hours to achieve protection. The lack of HIV–1 DNA, corresponding to the gag region in cells incubated with the virus and CRDS and the inhibition of infection after addition of 2',3'–dideoxyinosine to cells treated with CRDS and HIV–1 for less than 24 hours, suggest that CRDS delays events that precede and/or include reverse transcription. Analysis of the effect of CRDS on binding of HIV–1 neutralizing antibodies to gp120 demonstrated that both the continuous epitopes on the V3 loop and the discontinuous CD4 binding site of gp120 represent targets for CDRS. This interaction of CRDS with functional gp120 domains suggests that CRDS interferes with the membrane fusion process during HIV–1 infection. Concentrations of CRDS that were protective against infection with T cell– and macrophage–tropic HIV–1 isolates had fewer suppressive effects on T cell function in comparison with the related compound, dextran sulfate.

I.C.iv–2
Inhibition of HIV–1 Infectivity With Curdlan Sulfate In Vitro.

Form: Journal Article.
Author: Kaneko, Y.; Yoshida, O.; Nakagawa, R.; Yoshida, T.; Date, M.; Ogihara, S.; Shioya, S.; Matsuzawa, Y.; Nagashima, N.; Irie, Y.; et al.
Source: Biochemical Pharmacology. 39(4):793–797, February 15, 1990.

Published Abstract: None.
Annotators' Abstract: Carrageenan, heparin, dextran sulfate, fucoidan, pentosan polysulfate, polysulfated polysylan, and mannan sulfate have shown anti–HIV activity in vitro. Using the findings in other sulfated polysaccharides against HIV infectivity, the authors evaluated curdlan sulfate to determine its inhibitory activity against HIV and its therapeutic availability in vitro. According to assay techniques, curdlan sulfate had prominent inhibitory activity against HIV at a concentration of $3.3 µg/ml, without any direct toxicity to cells up to a CRDS concentration of 5000 µg/ml. The activity of curdlan sulfate was also assessed by using curdlan sulfate–depleted cell culture after incubation with MT–4/HIV, MT04 cells and by using curdlan sulfate for different periods of time. The HIV cellular infectivity disappeared completely in curdlan sulfate–depleted cell culture after incubation for 168 hours at a curdlan sulfate concentration of $5 µg/ml. The results achieved from half life, anticoagulant activity, and antigenicity suggest that it would be worthwhile to investigate curdlan sulfate in AIDS clinical research with further safety and toxicologic testing.

I.C.*v.* Preclinical Studies of Polysaccharide Microbicides–Other.

I.C.v–1
Novel Sulfated Polysaccharides: Dissociation of Anti–Human Immunodeficiency Virus Activity From Antithrombin Activity.

Form: Journal Article.
Author: Baba, M.; De Clercq, E.; Schols, D.; Pauwels, R.; Snoeck, R.; Van Boeckel, C.; Van Dedem, G.; Kraaijeveld, N.; Hobbelen, P.; Ottenheijm, H.; et al.
Source: Journal of Infectious Diseases. 161(2):208–213, February 1990.

Published Abstract: Novel sulfated polysaccharides, sulfated bacterial glycosaminoglycan (Org 31581) and chemically degraded heparin (Org 31733), have proved to be potent and selective inhibitors of human immunodeficiency virus (HIV) in vitro. Their 50% inhibitory concentrations for HIV type 1 (HIV–1) in MT–4 cells were 0.67 and 0.52 µg/ml, respectively. These values are comparable to those obtained for dextran sulfate and standard heparin (0.39 and 0.89 µg/ml, respectively). Org 31581 and Org 31733 showed much less antithrombin activity than did dextran sulfate and standard heparin. These results indicate that the anti–HIV activity of sulfated polysaccharides can be dissociated from their antithrombin activity. Org 31581 and Org 31733 were equally inhibitory to HIV–2 and HIV–1 and were also inhibitory to the replication of human cytomegalovirus. Syncytium formation, induced by cocultivation of MOLT–4 (clone 8) cells with chronically HIV–1–infected HuT 78 cells, was additionally inhibited by Org 31581. As previously demonstrated with dextran sulfate and heparin, both Org 31581 and Org 31733 blocked virus adsorption to the host cells. These compounds offer great promise as candidate drugs for the chemotherapy of HIV infections.

I.C.v–2
Pentosan Polysulfate, a Sulfated Oligosaccharide, is a Potent and Selective Anti–HIV Agent In Vitro.

Form: Journal Article.
Author: Baba, M.; Nakajima, M.; Schols, D.; Pauwels R.; Balzarini, J.; De Clercq, E.
Source: Antiviral Research. 9(6):335–343, September 1988.

Published Abstract: Several sulfated oligo– or polysaccharides, such as pentosan polysulfate; fucoidan; dextran sulfate; heparin; and iota–, kappa– and lambda–carrageenans, proved to be potent and selective inhibitors of human immunodeficiency virus type 1 (HIV–1) in vitro. The most potent anti–HIV–1 activity was recorded for the oligosaccharide pentosan polysulfate, its 50% antiviral effective dose (ED_{50}) being 0.19 µg/ml in MT–4 cells. It inhibited HIV–1 antigen expression in HUT–78 cells at an ED_{50} of 0.02 µg/ml, and complete inhibition of HIV–1 antigen expression was obtained at a concentration of 4.0 µg/ml. No toxicity for MT–4 cells was observed with pentosan polysulfate at a concentration of 2,500 µg/ml. The anticoagulant activity of pentosan polysulfate was more than tenfold lower than that of heparin (14.4 and 177 U/mg, respectively). In fact, pentosan polysulfate achieved its anti–HIV–1 activity at a concentration 370–fold below its anticoagulant threshold (1 U). Pentosan polysulfate inhibits virus adsorption to the cells, as was demonstrated by monitoring the association of radiolabeled HIV–1 virions with MT–4 cells.

I.C.v–3
Anti–Human Immunodeficiency Virus Type 1 Activity of Sulfated Monosaccharides: Comparison With Sulfated Polysaccharides and Other Polyions.

Form: Journal Article.
Author: Bagasra, O.; Whittle, P.; Heins, B.; Pomerantz, R. J.
Source: Journal of Infectious Diseases. 164(6):1082–90, December 1991.

Published Abstract: Previously reported were the anti–human immunodeficiency virus type 1 (HIV–1) activities of four sulfated polysaccharides: dextran sulfate, pentosan polysulfate, chondroitin sulfate, and heparin sulfate. This study evaluates the anti–HIV–1 activities of several other sulfated polysaccharides, monosaccharides, neutral polysaccharides, and polypeptides. Anti–HIV–1 activities of these various agents were

measured by four different assays: (1) HIV–1–induced syncytia formation; (2) infectivity of cell–free HIV–1 after preincubation with the putative anti–HIV–1 agent; (3) protective ability of the agents for target CD4+ cells; and (4) anti–reverse transcriptase activity. In addition, potential toxicity of the putative anti–HIV–1 agents was measured by the agents' effects on cellular proliferation, cytotoxicity, and coagulation processes. These data indicate that only sulfated polysaccharides and one sulfated monosaccharide, glucosamine 6–sulfate, have significant anti–HIV–1 activity. The therapeutic potentials of these agents also are discussed, with special reference to absorption of glucosamine 6–sulfate through the gastrointestinal tract.

I.C.v–4

The V3 Region of the Envelope Glycoprotein of Human Immunodeficiency Virus Type 1 Binds Sulfated Polysaccharides and CD4–Derived Synthetic Peptides.

Form: Journal Article.
Author: Batinic, D.; Robey, F. A.
Source: Journal of Biological Chemistry. 267(10):6664–71, April 5, 1992.

Published Abstract: The glycoprotein gp120 is the envelope glycoprotein found on the surface of human immunodeficiency virus type 1 (HIV–1), binding to human cell surface CD4 receptors to initiate the HIV–1 infection process. It is now well–established that synthetic peptides from the V3 region on gp120 elicit antibodies that block HIV–1 infection and HIV–1–mediated cell fusion. The authors show that synthetic peptides derived from similar V3 regions of several isolates of HIV–1 bind [^{3}H]heparin and demonstrate that [^{3}H]heparin binds to recombinant gp120 IIIB. The binding could be blocked by unlabeled heparin, dextran sulfate, and by a highly anionic benzylated synthetic peptide derived from human CD4 (amino acids 81–92). The nonbenzylated peptides from the same region were considerably less active. Unlabeled heparin, dextran sulfate, and the CD4–derived peptides were able to compete with the binding of soluble gp120 to immobilized antibodies against fragments of the V3 from isolate IIIB, but they had no effect on the binding of gp120 to antipeptide antibodies targeted against another unrelated region of gp120. Biotin conjugated to the benzylated CD4–peptide bound to gp120 and was blocked from this binding by anti–V3 antibodies. These results indicate that the three materials that have been demonstrated by others to block HIV–1 infection in vitro—sulfated polysaccharides, certain CD4–derived synthetic peptides, and anti–V3 antibodies—may be acting through a common mechanism that includes binding to the V3 region of gp120 on HIV–1.

I.C.v–5

In Vitro Activity of Mannan Sulfate, a Novel Sulfated Polysaccharide, Against Human Immunodeficiency Virus Type 1 and Other Enveloped Viruses.

Form: Journal Article.
Author: Ito, M.; Baba, M.; Hirabayashi, K.; Matsumoto, T.; Suzuki, M.; Suzuki, S.; Shigeta, S.; De Clercq, E.
Source: European Journal of Clinical Microbiology and Infectious Diseases. 8(2):171–173, February 1989.

Published Abstract: Mannan sulfate, a novel sulfated polysaccharide, was prepared and investigated for its activity against human immunodeficiency virus type 1 (HIV–1) in vitro. Mannan sulfate totally inhibited HIV–1–induced cell destruction and viral antigen expression in HIV–1–infected MOLT–4 (clone 8) cells at a concentration of 4 µg/ml. The antiviral 50% effective doses (ED_{50}) obtained with mannan sulfate in MOLT–4 (clone 8) cells and in MT–4 cells were 1.5 and 9.3 µg/ml, respectively. No toxicity for MOLT–4 (clone 8) cells or MT–4 cells was observed at a concentration of 4,000 and 2,500 µg/ml, respectively. Mannan sulfate was also inhibitory to other enveloped viruses, namely, herpes simplex virus types 1 and 2, vaccinia virus, and vesicular stomatitis virus. These results suggest that mannan sulfate may be useful for the chemotherapy of various viral infections, including those causing and associated with acquired immunodeficiency syndrome.

I.C.v–6

Anti–HIV Type 1 Properties of Chemically Modified Heparins With Diminished Anticoagulant Activity.
Author: Lopalco, L.; Ciccomascolo, F.; Lanza, P.; Zoppetti, G.; Caramazza, I.; Leoni, F.; Beretta, A.; Siccardi, A. G.

[See abstract I.C.ii–4.]

I.C.v–7
Investigations Into the Mechanism by Which Sulfated Polysaccharides Inhibit HIV Infection In Vitro.

Form: Journal Article.
Author: McClure, M. O.; Moore, J. P.; Blanc, D. F.; Scotting, P.; Cook, G. M.; Keynes, R. J.; Weber, J. N.; Davies, D.; Weiss, R. A.
Source: AIDS Research and Human Retroviruses. 8(1):19–26, January 1992.

Published Abstract: Sulfated polysaccharides have been shown to inhibit human immunodeficiency virus (HIV) infection in vitro. Dextrin sulfate, fucoidan, and dextran sulfate fail to neutralize virions directly, but interact with target cells to inhibit virus entry. Ionic interactions of sulfated polyanions with oppositely charged cell surface components, including CD4, have been assumed to be the inhibitory mechanism. The authors show that the sulfated polysaccharides inhibit infection of both CD4+ and CD4– cell lines by HIV and that they inhibit human T–lymphotropic virus I (HTLV–I) and, to a lesser extent, the simian retrovirus, MPMV, which uses receptors other than CD4. One binding site for radiolabeled fucoidan on the surface of human T cells is an 18–kD protein, but its significance is not yet clear.

I.C.v–8
N–Carboxymethylchitosan–N–O–Sulfate as an Anti–HIV–1 Agent.

Form: Journal Article.
Author: Sosa, M. A.; Fazely F.; Koch, J. A.; Vercellotti, S. V.; Ruprecht, R. M.
Source: Biochemical and Biophysical Research Communications. 174(2):489–496, January 31, 1991.

Published Abstract:
N–carboxymethylchitosan–N–O–sulfate (NCMCS), a sulfated polysaccharide derivative of chitin, is shown to inhibit the propagation of the human immunodeficiency virus type 1 (HIV–1) in human CD4+ cells and the propagation of Rauscher murine leukemia virus (RLV) in murine fibroblasts. A dose–dependent inhibition of both viruses was observed without significant cytotoxicity. NCMCS blocked the binding of HIV–1 to human CD4+ target cells and competitively inhibited HIV–1 reverse transcriptase. Thus, NCMCS may prevent HIV–1 infection by inhibiting viral adsorption to the CD4 receptor and reverse transcription of the viral genome.

I.C.v–9
Sulfated Alkyl Oligosaccharides With Potent Inhibitory Effects on Human Immunodeficiency Virus Infection.

Form: Journal Article.
Author: Uryu, T.; Ikushima, N.; Katsuraya, K.; Shoji, T.; Takahashi, N.; Yoshida, T.; Kanno, K.; Murakami, T.; Nakashima, H.; Yamamoto, N.
Source: Biochemical Pharmacology. 43(11):2385–92, June 9, 1992.

Published Abstract: Compounds with medium relative molecular masses active against human immunodeficiency virus (HIV) were synthesized. Sulfated alkyl oligosaccharides, such as sulfated octadecyl maltohexaoside, sulfated dodecyl laminaripentaoside, and sulfated dodecyl laminari–oligomer, caused 50% inhibition of virus infection in the 50% effective concentration (EC_{50}) range of 0.4–0.7 µg/ml in vitro using the MT–4 cell line and human immunodeficiency virus type 1 (HIV–1)/human T–lymphotropic virus IIIB (HTLV–IIIB) virus isolate, though sulfated oligosaccharides without alkyl groups showed low anti–HIV activity. This anti–HIV activity was close to the EC_{50} of 0.43 µg/ml for the highly active sulfated polysaccharide curdlan sulfate, which was reported to inhibit HIV infection completely at a concentration as low as 3.3 µg/ml. These compounds were also active against human immunodeficiency virus type 2 (HIV–2) and a clinically isolated HIV–1 with reduced azidothimidine sensitivity. For such sulfated alkyl oligosaccharides, the mechanism of inhibition of HIV infection was assumed to be the inhibition of HIV binding to the cell and, to some extent, the interaction of the alkyl portion with the lipid bilayer of the virus.

Commentary: This has been proposed as a potential vaginal microbicide.

I.C.v–10
Sulphoevernan, a Polyanionic

Polysaccharide, and the Narcissus Lectin Potently Inhibit Human Immunodeficiency Virus Infection by Binding to Viral Envelope Protein.

Form: Journal Article.
Author: Weiler, B. E.; Schroder, H. C.; Stefanovich, V.; Stewart, D.; Forrest, J. M.; Allen, L. B.; Bowden, B. J.; Kreuter, M. H.; Voth, R.; Muller, W. E.
Source: Journal of General Virology. 71(Pt 9):1957–63, September 1990.

Published Abstract: Sulphoevernan is a sulfated alpha–1–3,1–4 polyglucan (relative molecular weight (M_r) 20,000) with a helical structure. This compound effectively inhibits both human immunodeficiency virus type 1 (HIV–1) and type 2 infection of cells in vitro at concentrations around 0.5 µg/ml. Moreover, the compound completely inhibits HIV–1–induced syncytium formation at a concentration of 1 µg/ml. Competition experiments with ^{35}S–labeled sulphoevernan revealed that the mannose–specific lectin from *Narcissus pseudonarcissus* prevented binding of sulphoevernan to HIV–1, whereas the antibody OKT4A did not reduce the amount of sulphoevernan bound to MT–2 cells. These data indicate that the noncytotoxic polymer sulphoevernan binds to the virus rather than to the host cell. In vivo studies, using Rauscher leukemia virus in NMRI mice, revealed that, at a daily dose of 20 mg/kg, the animals were protected against virus–induced increases in spleen weight. From these in vitro and in vivo data, the authors conclude that sulphoevernan has potential in the treatment of acquired immunodeficiency syndrome.

I.D. Preclinical Studies–Povidone Iodine.

I.D–1
The Effect of Chemical Intravaginal Contraceptives and Betadine® on *Ureaplasma urealyticum*.

Form: Journal Article.
Author: Amortegui, A. J.; Melder, R. J.; Meyer, M. P.; Singh, B.
Source: Contraception. 30(2):135–141, August 1984.

Published Abstract: The purpose of this study was to find a barrier contraceptive agent capable of controlling infections and sexual transmission of *Ureaplasma urealyticum* from the female genital tract, especially to help reduce nongonococcal urethritis in males caused by this organism. Therefore, the in vitro antimicrobial activity of six intravaginal contraceptives and Betadine® against the eight serotypes of the organism was investigated. The results indicate that some of these contraceptives produce partial inhibition of *Ureaplasma* at low dilutions, while Betadine® produces a ureaplasmacidal effect up to dilutions of 1:64. These effects do not appear to be primarily the result of the pH of these agents. Thus, some of these agents may have a potential role in controlling transmission of *U. urealyticum*.

I.D–2
Inactivation of Human Immunodeficiency Virus by Betadine® Products and Chlorhexidine.

Form: Journal Article.
Author: Harbison, M. A.; Hammer, S. M.
Source: Journal of Acquired Immune Deficiency Syndromes. 2(1):16–20, 1989.

Published Abstract: Eleven products containing povidone–iodine (Betadine®) and chlorhexidine gluconate solution were tested for their ability to inactivate human immunodeficiency virus (HIV) in a cell culture system. All Betadine® products completely inactivated the virus at povidone–iodine concentrations of $0.5% (10– to 20–fold dilutions of stock) except for Betadine® Lubricating Antiseptic Gel, which required 2.5% for efficacy (1:2 dilution). Chlorhexidine gluconate completely inactivated HIV at concentrations of $0.2% (1:100 dilution of laboratory stock; 1:20 dilution of commercial stock). Betadine® douche and medicated douche did not inactivate HIV at the concentrations recommended for clinical use (0.33% and 0.25%, respectively) but were effective at povidone–iodine concentrations of 0.5%. Inactivation appeared to be immediate, since no difference in efficacy based on length of exposure to the microbicide was detected. Thus, both microbicides are highly effective in killing HIV in vitro.

I.D–3
Inactivation of Papilloma Virus by Low Concentrations of Povidone–Iodine.

Form: Journal Article.
Author: Sokal, D. C.; Hermonat, P. L.
Source: Sexually Transmitted Diseases. 22(1):22–24, January–February 1995.

Published Abstract: A recent report by Hermonat et al. showed that nonoxynol–9 is completely inactive against bovine papilloma virus, which is very closely related to human papilloma virus. Finding a vaginal microbicide active against human papilloma virus that would reduce the risk of its sexual transmission would be desirable. Objective: To determine whether povidone–iodine is active in vitro against bovine papilloma virus. Methods: The authors prepared a bovine papilloma virus–1 stock by extraction of a fibropapilloma and treated it with various concentrations of povidone–iodine. The virus/povidone–iodine samples were incubated at 37EC for 15 minutes and then placed on contact–inhibited cells of mouse fibroblast line C127 in 10–cm tissue culture dishes for the transformation assay. At 2 weeks after infection, oncogenic foci induced by bovine papilloma virus appeared and were counted after the cells were fixed with 4% formaldehyde and stained with methylene blue. Results: Approximately 90% inactivation of papilloma virus was demonstrated with exposure to 0.1% povidone–iodine, and 99.9% inactivation was seen at 0.3%. Conclusions: The concentrations of povidone–iodine that were effective in this study are lower than the concentrations in available over–the–counter preparations of povidone–iodine. Additional research is needed to verify whether papilloma virus is susceptible to other, more acceptable agents. Clinical trials

may be warranted to determine whether povidone–iodine or other agents would reduce the rate of sexual transmission of the strains of human papilloma virus associated with cervical cancer.

I.E. Preclinical Studies–Gossypol.

I.E–1
Selective Inhibition of Human Immunodeficiency Virus Type 1 Replication by the (–) but not the (+) Enantiomer of Gossypol.

Form: Journal Article.
Author: Lin, T. S.; Schinazi, R.; Griffith, B. P.; August, E. M.; Eriksson, B. F.; Zheng, D. K.; Huang, L. A.; Prusoff, W. H.
Source: Antimicrobial Agents and Chemotherapy. 33(12):2149–51, December 1989.

Published Abstract: The (–) enantiomer of gossypol, but not the (+) enantiomer, had good antiviral activity in peripheral blood mononuclear cells against human immunodeficiency virus type 1 at a concentration more than twentyfold lower than that required for cytotoxicity. However, in H9 cells, the (–) enantiomer, although more potent as an antiviral agent, was also more cytotoxic.

I.E–2
Anti–HIV–1 Activity and Cellular Pharmacology of Various Analogs of Gossypol.

Form: Journal Article.
Author: Lin, T. S.; Schinazi, R. F.; Zhu, J.; Birks, E.; Carbone, R.; Si, Y.; Wu, K.; Huang, L.; Prusoff, W. H.
Source: Biochemical Pharmacology. 46(2):251–255, July 20, 1993.

Published Abstract: The authors previously reported that the racemic mixture and both enantiomers of gossypol inhibit the replication of human immunodeficiency virus type 1 (HIV–1) (Lin et al., Antimicrobial Agents and Chemotherapy 33:2149–2151, 1989). The present study evaluates the activities of a variety of analogs of gossypol as well as a few nongossypol analogs. Compounds 2, 3, 10, and 13 were slightly more inhibitory than (–) gossypol to the replication of HIV–1 in cell culture. Compounds 4 and 8 were cytotoxic to human peripheral blood monocyte (PBM) cells, and compounds 2 and 3 were cytotoxic to Vero cells but not PBM cells. The effects of the two enantiomers of gossypol on the cell volume and migration of H9 cells through the cell cycle were evaluated during 72 hours of incubation. The (–) enantiomer of gossypol was more toxic to H9 cells than the (+) enantiomer of gossypol, as evidenced by cell destruction. Prior to cell destruction, there appeared to be no significant effect on cell cycle distribution with either enantiomer.

I.E–3
Inactivation of Human Immunodeficiency Virus In Vitro by Gossypol.

Form: Journal Article.
Author: Polsky, B.; Segal, S. J.; Baron, P. A.; Gold, J. W.; Ueno, H; Armstrong, D.
Source: Contraception. 39(6):579–587, June 1989.

Published Abstract: Gossypol, a polyphenolic aldehyde extracted from cottonseed, is a male antifertility agent that has been reported to have antiviral activity. The authors report that gossypol inactivates human immunodeficiency virus (HIV) in an in vitro system. Following exposure of cell–free incubates of HIV to 100 FM ultracentrifuged gossypol, and inoculation of the washed pellet onto H–9 cells, there is no evidence of elevated reverse transcriptase activity over 21 days. Treatment with lower concentrations of gossypol reduces the peak and lengthens the time to maximal reverse transcriptase activity as compared with control cultures. These observations suggest that gossypol could be used as a vaginal spermicidal/virucidal agent. The mechanism of the in vitro antiviral action as well as the effect of orally administered gossypol on the infectivity of semen of HIV–seropositive men warrant further study.

I.E–4
Antiviral Activities of Gossypol and its Derivatives Against Herpes Simplex Virus Type II.

Form: Journal Article.
Author: Radloff, R. J.; Deck, L. M.; Royer, R. E.; Vander Jagt, D. L.
Source: Pharmacological Research Communications. 18(11):1063–73, November

1986.

Published Abstract: Gossypol, a disequiterpene obtained from cottonseed oil, and a series of peri–acylated gossylic nitriles were compared for their antiviral activities against herpes simplex virus type 2 (HSV–2) and for their toxicities to the host Vero cells. All of the peri–acylated gossylic nitriles exhibited lower cytotoxicities to the host cell than did the parent compound gossypol. Both gossypol and the series of derivatives exhibited antiviral activities against HSV–2 when the virus was treated with the drug at concentrations as low as 5×10^{-7} M. Two of the derivatives, gossylic nitrile–1,1'–diacetate and gossylic nitrile–1,1'–divalerate, were capable of inhibiting viral multiplication in Vero cells that were infected with virus before administration of the drug. The results of this study indicate that modification of the aldehyde functional groups on gossypol lowers the toxicity of this drug but does not abolish its antiviral properties. Derivatives of gossypol may be useful antiviral agents.

I.E–5
Inhibition of Human Immunodeficiency Virus Type I Replication by Derivatives of Gossypol.

Form: Journal Article.
Author: Royer, R. E.; Mills, R. G.; Deck, L. M.; Mertz, G. J.; Vander Jagt, D. L.
Source: Pharmacological Research. 24(4):407–412, December 1991.

Published Abstract: Gossypol (I) and its derivatives gossylic nitrile–1,1'–diacetate (II), gossylic iminolactone (III), and gossylic lactone (IV) inhibit the replication of human immunodeficiency virus type 1 in vitro in the following order: III greater than I greater than II, IV. This indicates that derivatives of gossypol can retain antiviral activities. All of the derivatives are less cytotoxic than gossypol.

I.F. Preclinical Studies–Lactobacillus.

I.F–1
The Relationship of Hydrogen Peroxide–Producing Lactobacilli to Bacterial Vaginosis and Genital Microflora in Pregnant Women.

Form: Journal Article.
Author: Hillier, S. L.; Krohn, M. A.; Klebanoff, S. L.; Eschenbach, D. A.
Source: Obstetrics & Gynecology. 79(3): 369–373, March 1992.

Authors' Abstract: Lactobacilli provide an important microbial defense against genital colonization of pathogens. The role of hydrogen peroxide (H_2O_2) in the control of genital microflora was explored in a cross–sectional study of 275 women in the second trimester of pregnancy. Vaginal cultures were obtained for detection of H_2O_2–positive and H_2O_2–negative lactobacilli and other members of the genital microflora. Compared with women with H_2O_2–negative lactobacilli, women colonized by H_2O_2–positive lactobacilli were less likely to have bacterial vaginosis, symptomatic candidiasis, and vaginal colonization by *Gardnerella vaginalis, Bacteroides, Peptostreptococcus, Mycoplasma hominis, Ureaplasma urealyticum,* and viridans streptococci (P # .05 for each comparison). In addition to the above organisms, women without vaginal lactobacilli were more likely than those women with H_2O_2–positive lactobacilli to have *Chlamydia trachomatis*, and less likely to be colonized by *Enterococcus* or coagulase–negative staphylococci (P < .05 for each comparison). Vaginal colonization by group B streptococci for *Escherichia coli* was not related to the presence of H_2O_2–positive lactobacilli. These data suggest that the presence of H_2O_2–positive lactobacilli in the vagina is inversely correlated with infection by some genital pathogens in pregnant women.

I.F–2
The Normal Vaginal Flora, H_2O_2–Producing Lactobacilli, and Bacterial Vaginosis in Pregnant Women.

Form: Journal Article.
Author: Hillier, S. L.; Krohn, M. A.; Rabe, L. K.; Klebanoff, S. J.; Eschenbach, D. A.
Source: Clinical Infectious Diseases. 16 Suppl 4:S273–81, June 1993.

Authors' Abstract: In this study of the vaginal flora of 171 pregnant women in labor at term, the flora was categorized as normal (Lactobacillus predominant), intermediate, or representative of bacterial vaginosis (BV) on the basis of a vaginal smear. BV was diagnosed in 39 women (23%); the vaginal flora was classified as normal in 50% of cases and as intermediate in 27%. H_2O_2–producing lactobacilli were recovered from 5% of women with BV, 37% of those with an intermediate flora, and 61% of those with a normal flora. H_2O_2–negative lactobacilli were equally frequent (57–65%) in all three groups. The microorganisms most frequently recovered from women with BV included *Gardnerella vaginalis, Prevotella bivia/disiens, Bacteroides ureolyticus, Prevotella corporis/Bacteroides levii, Fusobacterium nucleatum, Mobiluncus sp., Peptostreptococcus prevotii, Peptostreptococcus tetradius, Peptostreptococcus anaerobius,* viridans streptococci*, Ureaplasma urealyticum,* and *Mycoplasma hominis* (P < .05 for each). The presence of all but three of these organisms was inversely related to vaginal colonization by H_2O_2–producing lactobacilli; the exceptions were *B. ureolyticus, F. nucleatum*, and *P. prevotii*. Other microorganisms were equally frequent among women with and without BV. We conclude that specific groups of anaerobes are associated with BV in this population and that a strong association exists between species associated with BV and those inhibited by H_2O_2–producing lactobacilli.

I.F–3
The In Vivo Effects of Nonoxynol–9 Contraception on Vaginal Microbial Flora and Colonization With *Escherichia coli*.

Form: Journal Article, Letter.
Author: Jones, B. M.; Eley, A.
Source: Journal of Infectious Diseases. 167(3):777–778, March 1993.

Published Abstract: None.
Annotators' Abstract: The authors isolated *Escherichia coli* from 16 of 66 (24%) spermicide

users but from only 14 of 113 (12%) persons who did not use spermicides. Of the 16 spermicide users whose cultures were positive for *E. coli*, 13 (81%) also had *Lactobacillus* species, whereas of the 14 persons who did not use spermicides but whose *E. coli* cultures were positive, only 6 (43%) had *Lactobacillus*.

I.F–4
In Vitro Antibacterial Activity of Antiseptics Against Vaginal Lactobacilli.

Form: Journal Article.
Author: Juliano, C.; Piu, L.; Gavini, E.; Zanetti, S.; Fadda, G.
Source: European Journal of Clinical Microbiology & Infectious Diseases. 11(12):1166–69, December 1992.

Authors' Abstract: The results of investigations carried out to evaluate the inhibitory activity in vitro of seven vaginal antiseptic douche solutions against several strains of vaginal lactobacilli isolated from asymptomatic women are reported. Some of the products examined showed marked antibacterial activity even at high dilutions and for short exposure times. The post–antibiotic effect of two of these antiseptics on vaginal lactobacilli was also evaluated. The results of these investigations suggest that uncontrolled use of antiseptic products could cause changes in the normal vaginal flora.

I.F–5
Effects of the Spermicidal Agent Nonoxynol–9 on Vaginal Microbial Flora.

Form: Journal Article.
Author: Klebanoff, S. J.
Source: Journal of Infectious Diseases. 165(1):19–25, January 1992.

Published Abstract: The use of nonoxynol–9–containing vaginal contraceptive preparations increases vaginal (and urethral) colonization by *Escherichia coli*. Nonoxynol–9 is toxic to various microorganisms, including *Lactobacillus acidophilus*, but has little or no direct effect on *E. coli*. *L. acidophilus*, which is present in the vaginas of most normal women, generates H_2O_2 which, when combined with peroxidase and a halide, was toxic to *E. coli*. This toxicity was inhibited by nonoxynol–9 due to the selective destruction of the lactobacilli. In contrast, at higher concentrations, nonoxynol–9 was toxic to *E. coli* when combined with peroxidase and a halide. This toxicity was shared with certain other nonionic detergents and was due to the formation of peroxides in the preparations on prolonged exposure to oxygen. *E. coli* colonization may, in part, reflect the balance between these opposing effects of nonoxynol–9 on the vaginal antimicrobial system. Damage to normal tissues by peroxides in nonoxynol–9 preparations needs to be considered further.

I.F–6
Viricidal Effect of *Lactobacillus acidophilus* on Human Immunodeficiency Virus Type 1: Possible Role in Heterosexual Transmission.

Form: Journal Article.
Author: Klebanoff, S. J.; Coombs, R. W.
Source: Journal of Experimental Medicine. 174(1):289–292, July 1, 1991.

Published Abstract: Peroxidase, H_2O_2, and a halide form a powerful antimicrobial system in phagocytes and tissue fluids, and certain microorganisms can serve as the source of H_2O_2 for this system. H_2O_2–generating *Lactobacillus acidophilus* (HPLB) is present in the vaginas of most healthy women and peroxidase has been detected in vaginal fluid. HPLB at high concentrations is virucidal to HIV–1; when levels of HPLB are ineffective alone, the addition of peroxidase (myeloperoxidase, eosinophil peroxidase) and a halide restores virucidal activity. HPLB can be replaced by H_2O_2 but not by non–H_2O_2–producing *L. acidophilus;* virucidal activity is also inhibited by azides and catalases. The survival of HIV in the female genital tract and thus, the likelihood of transmission, may be influenced by the activity of the HPLB peroxidase–halide system in the vagina.

I.F–7
Hydrogen Peroxide Production by *Lactobacillus* Species: Correlation With Susceptibility to the Spermicidal Compound Nonoxynol–9.

Form: Journal Article.
Author: McGroarty, J. A.; Tomeczek, L.; Pond, D. G.; Reid, G.; Bruce, A. W.
Source: Journal of Infectious Diseases. 165(6):1142–44, June 1992.

Published Abstract: Facultative anaerobic lactobacilli were recovered from the vaginas of 96.8% of 63 nonpregnant, healthy, premenopausal women. The predominant species were *Lactobacillus jensenii*, *Lactobacillus acidophilus*, and *Lactobacillus casei*. Of the women, 74.6% had hydrogen peroxide–producing lactobacilli, 22.2% had non–hydrogen peroxide–producing lactobacilli, and 3.2% had no lactobacilli. None of the 68 isolates had catalase activity. Some 68.2% of the isolates were inhibited by concentrations of #1% (wt/vol) of nonoxynol–9 (bactericidal for 73.3% of the isolates, bacteriostatic for 26.7%). The remaining 31.8% could grow in all concentrations to 25% (wt/vol) of nonoxynol–9. All of the lactobacilli that were sensitive to nonoxynol–9 produced hydrogen peroxide, whereas only 3 of 21 resistant strains were hydrogen peroxide producers. A significant correlation ($P < 0.001$, chi–square test) was found between hydrogen peroxide production and sensitivity to nonoxynol–9. It is suggested that the vaginal flora of spermicide users could be depleted of hydrogen peroxide–producing lactobacilli, possibly increasing susceptibility to urogenital infection.

I.F–8

Correlation Between Hydrophobicity and Resistance to Nonoxynol–9 and Vancomycin for Urogenital Isolates of Lactobacilli.

Form: Journal Article.
Author: Tomeczek, L.; Reid, G.; Cuperus, P. L.; McGroarty, J. A.; Van der Mei, H. C.; Bruce, A. W.; Khoury, A. E.; Busscher, H. J.
Source: FEMS Microbiology Letters. 73(1–2):101–104, July 1, 1992.

Authors' Abstract: Seven clinical isolates of lactobacilli were found to be relatively hydrophobic with a mean water–contact angle of 66 ± 15 degrees, and to be susceptible to 1% nonoxynol–9 and vancomycin. However, seven other strains were relatively hydrophilic with a mean water–contact angle of 32 ± 13 degrees, and found to be resistant to 25% nonoxynol–9 and vancomycin. Thus, the surface properties of lactobacilli that influence susceptibility to antimicrobial agents may involve surface hydrophobicity. Possibly the penetration barrier posed by the cell surface towards these two nonionic antimicrobials is lower for hydrophobic cells than for hydrophilic cells.

I.G. Preclinical Studies–Reverse Transcriptase Inhibitors.

I.H. Preclinical Studies–New Candidate Compounds.

I.H–1
Report to the National Advisory Child Health and Human Development Council, June 5, 1995.
Author: Anonymous.
[See IV.A–2.]

I.H–2
Effects of Tampon Components on Growth and Dissemination of *Neisseria gonorrhoeae*.

Form: Journal Article.
Author: Arko, R. J.; Wong, K. H.; Finley–Price, K. G.; Rasheed, J. K.
Source: British Journal of Venereal Diseases. 58(2):105–108, April 1982.

Published Abstract: Six components used in vaginal tampons were tested for their effects on a strain of *Neisseria gonorrhoea*e isolated from a patient with disseminated infection. Tampon components containing carboxymethyl cellulose or its derivative prolonged the in vitro survival of gonococci and, when injected with mucin into mice, significantly ($P < 0.0001$) increased the dissemination of gonococci from the peritoneal cavity. In contrast, a component extracted from rayon tampons reduced in vitro survival and appeared to suppress gonococcal dissemination in mice. Since tampons are used by a large number of women at a time when the risk of developing complications from venereal infections is increased, their effects on potential urogenital pathogens warrant further study.

I.H–3
The Mannose–Specific Plant Lectins From *Cymbidium hybrid* and *Epipactis helleborine* and the (N–Acetylglucosamine)n–Specific Plant Lectin From *Urtica dioica* are Potent and Selective Inhibitors of Human Immunodeficiency Virus and Cytomegalovirus Replication In Vitro.

Form: Journal Article.
Author: Balzarini, J.; Neyts, J.; Schols, D.; Hosoya, M.; Van Damme, E.; Peumans, W.; De Clercq, E.
Source: Antiviral Research. 18(2):191–207, June 1992.

Published Abstract: A series of 4 mannose–specific, 3 *N*–acetylglucosamine (GlcNAc)n–specific, 10 *N*–acetylgalactosamine/ galactose(GalNAc/Gal)–specific, one 5–acetylneuraminic acid (alpha–2,3 Gal/GalNAc)–specific, and one 5–acetylneuroaminic acid (alpha–2,6–Gal/Gal–NAc)–specific plant agglutinins were evaluated for their antiviral activity in vitro. The mannose–specific lectins from the orchid species *Cymbidium hybrid*, *Epipactis helleborine*, and *Listera ovata* were highly inhibitory to human immunodeficiency virus type 1 (HIV–1) and type 2 (HIV–2) in MT–4 cells, and showed marked antihuman cytomegalovirus (CMV), respiratory syncytial virus (RSV), and influenza A virus activity in HEL, HeLa, and MDCK cells, respectively. The 50% effective concentration (EC_{50}) of *C. hybrid* and *E. helleborine* for HIV ranged from 0.04 to 0.08 µg/ml, that is, about three orders of magnitude below their toxicity threshold (50% inhibitory concentration for MT–4 cell growth: 54–60 µg/ml). Also, the (GlcNAc)n–specific lectin from *Urtica dioica* was inhibitory to cytopathicity induced by HIV–1, HIV–2, CMV, RSV, and influenza A virus at an EC_{50} ranging from 0.3 to 9 µg/ml. The GalNAc/Gal–, alpha–2,3–Gal/GalNAc–, or alpha–2,6–Gal/GalNAc–specific lectins were not inhibitory to HIV or CMV at nontoxic concentrations. *C. hybrid*, *E. helleborine*, and *U. dioica* proved to be potent inhibitors of syncytium formation between persistently HIV–1– and HIV–2–infected HUT–78 cells and CD4+ MOLT/4 (clone 8) cells (EC_{50}, 0.2–2 µg/ml). Unlike dextran sulfate, the plant lectins *C. hybrid*, *E. helleborine*, and *U. dioica*, did not interfere with HIV–1 adsorption to MT–4 cells or with RSV and influenza A virus adsorption to HeLa and MDCK cells, respectively. They presumably interact at the level of virion fusion with the target cell.

I.H–4
Inhibition of Intracellular *Histoplasma capsulatum* Replication by Murine Macrophages That Produce Human Defensin.

Form: Journal Article.
Author: Couto, M. A.; Liu, L.; Lehrer, R. I.;

Ganz, T.
Source: Infection & Immunity. 62(6):2375–78, June 1994.

Published Abstract: Although purified defensins are effective microbicides in vitro, their operation within intact phagocytes has not been established. To address this question, we inserted cDNA–encoding human defensin HNP-1 into a pBabe/neo retroviral vector and transduced it into RAW 264.7 cells, a murine macrophage line that lacks endogenous defensins. We isolated five independent clones of HNP-1-transduced cells, all of which secreted prodefensin and contained small amounts of fully processed HNP-1. The two clones that produced the largest amounts of defensin (clones 5 and 14), together with wild-type RAW cells and pBabe/neo-transduced RAW cells (control), were used for the present study. All cells were grown in Dulbecco's modified Eagle's medium-F12 medium that contained 10% heat-inactivated fetal bovine serum and gentamicin. The medium used for the transduced cells contained aminoglycoside G418 in lieu of gentamicin. Both wild-type and transduced cells were placed in antibiotic-free medium 96 hours prior to challenge with a yeast-phase strain of *Histoplasma capsulatum*. Phagocytosis of yeast cells was allowed to proceed for 90 minutes and was followed by washing and further incubation for 18.5 hours. Whereas the phagocytic index did not differ significantly among the four cell populations under study, the mean level of intracellular growth of *H. capsulatum* in the defensin-transduced RAW cells was significantly lower than those observed for any other cell types ($P < 0.05$). These findings constitute the first instance of xenogeneic expression of an antimicrobial peptide by phagocytes and suggest that macrophages can be armed with defensins to enhance their ability to restrict certain intracellular pathogens.

I.H–5
Studies on the Contraceptive Efficacy of Praneem Polyherbal Cream.

Form: Journal Article.
Author: Garg, S.; Taluja, V.; Upadhyay, S. N.; Talwar, G. P.
Source: Contraception. 48(6):591–596, December 1993.

Published Abstract: Praneem polyherbal cream, a spermicidal formulation, developed and used by the National Institute of Immunology, is a purified extract formulated from the dried seeds of an ancient Indian plant *Azadirachta indica* (Neem), extract from the pericarp of fruits of the *Sapindus* species, and quinine hydrochloride. These ingredients have a synergistic spermicidal activity, and an optimized formula was derived. The components were made into a water–soluble cream base prepared by stabilizing a pharmaceutically acceptable base with the addition of intraperitoneal (IP) grade antioxidant and preservatives. The cream is devoid of irritation and sensitization potential, as seen with the standard Draize test on normal and abraded skin of rabbits and by a 21–day cumulative skin sensitivity test in human volunteers. The formulation was found to be safe under subacute toxicity studies in monkeys and was shown to have high contraceptive efficacy in rabbits and monkeys after intravaginal application. The shelf–life of the cream at room temperature is estimated to be 18 months by accelerated stability studies.

Commentary: Neem has been proposed as a potential vaginal microbicide.

I.H–6
Potent In Vitro Anti–Human Immunodeficiency Virus–1 Activity of Modified Human Serum Albumins.

Form: Journal Article.
Author: Jansen, R. W.; Molema, G.; Pauwels, R.; Schols, D.; De Clercq, E.; Meijer, D. K.
Source: Molecular Pharmacology. 39(6):818–823, June 1991.

Published Abstract: A series of neoglycoproteins was synthesized by coupling of thiophosgene–activated p–aminophenyl derivatives (Biology of the Cell 47:95–110, 1983; Journal of Histochemistry and Cytochemistry 32:1091–1094, 1984) of various sugars to human serum albumin. The compounds were evaluated for their in vitro activity against human immunodeficiency virus (HIV). Neoglycoproteins with the highest sugar content were found to be the most potent inhibitors of HIV–1–induced cytopathogenicity. However, this was not due to the nature of the sugar used but, rather, was related to the extra

negative charge of the neoglycoproteins. To investigate whether the antiviral activity of the neoglycoproteins exhibited sugar specificity, increased with increasing negative charge, or depended on both sugar specificity and negative charge, the authors synthesized albumins and neoglycoproteins with an enhanced negative charge by treatment with formaldehyde or succinic anhydride. Succinylated human serum albumin had the most pronounced net negative charge and had a 50% inhibitory concentration (IC_{50}) of about 1 µg/ml. No cytotoxicity was observed at concentrations up to 1 mg/ml, implicating a selectivity index (50% cytotoxic concentration (CC_{50})/IC_{50}) of at least 10^3. To elucidate the mechanism of action of these anionic albumins, the authors investigated whether they interfered with HIV–1 adsorption to the cells, binding of anti–OKT4A monoclonal antibody (mAb) to the CD4 receptor, binding of anti–gp120 mAb to gp120, or inhibition of syncytium formation in cocultures of HIV–1–infected HUT–78 cells with MOLT–4 cells. From these experiments, the authors conclude that albumins with an increased negative charge are potent and nontoxic anti–HIV–1 agents; that they cause a 50% reduction in syncytium formation in the same concentration range as their IC_{50} in the antiviral assay; that they do not bind to the OKT4A epitope of the CD4 receptor; and that they only partly inhibit anti–gp120 mAb–gp120 interaction and virus–cell binding at concentrations that are 100 times higher than their IC_{50} in the antiviral assay. Therefore, the authors conclude that the modified albumins interfere with a postbinding event, of which one of the potential mechanisms is an interaction with the gp41 fusion protein, necessary for syncytium formation but not involved in initial virus binding.

I.H–7

Novel, Negatively Charged, Human Serum Albumins Display Potent and Selective In Vitro Anti–Human Immunodeficiency Virus Type 1 Activity.

Form: Journal Article.
Author: Jansen, R. W.; Schols, D.; Pauwels, R.; De Clercq, E.; Meijer, D. K.
Source: Molecular Pharmacology. 44(5):1003–7, November 1993.

Published Abstract: The authors prepared a series of modified proteins and peptides by derivatizing the positively charged epsilon–amino groups of the lysine amino acids through reaction with anhydrides of succinic acid (Suc) and aconitic acid (Aco). Human serum albumin (HSA) was modified by introduction of a single carboxylic group (Suc–HSA) or two carboxylic groups (Aco–HSA) per amine function, yielding strongly negatively charged compounds. The in vitro anti–human immunodeficiency virus type 1 (HIV–1) inhibitory concentration (IC_{50}) of Suc–HSA was about 1 µg/ml, and the most polyanionic modified albumin of the series (Aco–HSA) exhibited an IC_{50} as low as 0.02 µg/ml. Similar derivatization of the plasma protein orosomucoid, or the synthetic polypeptide polylysine, did not produce compounds with significant anti–HIV–1 activity, indicating an HSA–specific effect. The mechanism of action of Suc–HSA was reported to be the inhibition of a post–binding, virus–cell fusion event, probably due to interference with the gp41–mediated fusion process. In the present study, the authors demonstrate that the more potent Aco–HSA interferes with this fusion process; additionally, this compound inhibits (1) the binding of soluble CD4 to HIV–infected cells, (2) the binding of HIV particles to MT–4 cells, and (3) the binding of anti–gp120 monoclonal antibody to the gp120 molecule. This indicates that Aco–HSA, apart from postbinding fusion, also inhibits virus–cell binding by shielding viral gp120. The simultaneous inhibition of binding and fusion may lead to a synergistic effect, explaining the extreme potency of Aco–HSA. The polyanionic HSAs are significantly less active against HIV–2 and do not interfere with the replication of feline immunodeficiency virus or 12 other DNA or RNA viruses, indicating an HIV–1–specific effect. In contrast, another polyanionic compound, the sulfated polysaccharide dextran sulfate, inhibits the replication of various viruses in a more nonspecific way, as a general polyanion. Dextran sulfate also exhibits strong anticoagulant activity, whereas Suc–HSA and Aco–HSA do not show this unwanted side effect.

I.H–8

Inhibition of Entry of HIV Into Cells by Poly(A).Poly(U).

Form: Journal Article.
Author: Krust, B.; Callebaut, C.; Hovanessian, A. G.
Source: AIDS Research and Human Retroviruses. 9(11):1087–90, November 1993.

Published Abstract: Polyadenylic–polyuridylic acid, referred to as poly(A).poly(U), is a synthetic, double–stranded RNA that has been shown to manifest both antitumoral and immunomodulatory activities. Previously, the authors reported that poly(A).poly(U) inhibits human immunodeficiency virus (HIV) infection in cell cultures. Here, they provide direct evidence to demonstrate that the inhibitory action of poly(A).poly(U) is through its capacity to prevent entry of HIV particles into CD4–positive T lymphocytes. Such inhibition of HIV entry is also observed in the case of other polyanions, such as heparin, dextran sulfate, and poly(I).poly(C). The mechanism of inhibition appears to occur after binding of HIV particles to the CD4 receptor molecules, because the binding of the external envelope glycoprotein of HIV–1 (gp120) is not affected significantly in the presence of poly(A).poly(U) or other polyanions. These results confirm the potential of poly(A).poly(U) as an antiviral drug against HIV infection.

I.H–9

Sulfated Polyanions Prevent HIV Infection of Lymphocytes by Disruption of the CD4–gp120 Interaction, but Do Not Inhibit Monocyte Infection.

Form: Journal Article.
Author: Lynch, G.; Low, L.; Li, S.; Sloane, A.; Adams, S.; Parish, C.; Kemp, B.; Cunningham, A. L.
Source: Journal of Leukocyte Biology. 56(3):266–272, September 1994.

Published Abstract: Sulfated polyanions (SPs) bind variably to lymphocyte–expressed CD4 and inhibit binding of monoclonal antibodies to the first two domains of CD4. To further define this interaction, soluble recombinant CD4 (sCD4; four extracellular domains), its truncated aminoterminal two–domain derivative, and three linear peptide analogues spanning residues 6–60 (6–24, 20–40, and 41–60) in the first domain were investigated for SP binding. Dextran sulfate (500 kDa), polyvinyl sulfate, fucoidan, and carrageenan–kappa, each immobilized on carboxymethyl cellulose fibers, bound strongly to both the two–domain and four–domain recombinant CD4 molecules (similar to that observed with native CD4), whereas dextran sulfate (5 kDa), chondroitin 6–sulfate, and pentosan sulfate bound relatively poorly. No peptide binding to SPs was observed. Recombinant gp120 bound poorly (<10%) to all of the immobilized polyanions, except pentosan sulfate (17%), for which some binding was noted. Binding of radiolabeled V3 loop peptide to SPs was slightly greater, with 20%–30% binding to polyvinyl sulfate, dextran sulfate (500 kDa), and pentosan sulfate. Competitive binding studies demonstrated the predominance of sCD4 rather than rgp120 binding to SPs, and supported previous data demonstrating a binding site for dextran sulfate (500 kDa) on the first domain of CD4 adjacent to the gp120 binding site and recognized by OKT4C and E monoclonal antibodies. Hence, disruption of the CD4–gp120 interaction is probably responsible for most of the observed antiviral activity of SPs toward human immunodeficiency virus (HIV) infection of lymphocytes. However, HIV infection and gp120 binding to monocytes were unaffected by SPs, probably because SPs were unable to block the CD4–gp 120 interaction in monocytes.

I.H–10

Bovine Beta-Lactoglobulin Modified by 3-Hydroxyphthalic Anhydride Blocks the CD4 Cell Receptor for HIV.

Form: Journal Article.
Author: Neurath, A. R.; Jiang, S.; Strick, N.; Lin, K.; Li, Y. Y.; Debnath, A. K.
Source: Nature Medicine. 2(2):230–234, February 1996.

Published Abstract: Sexual transmission is the most frequent (86%) route of adult HIV-1 transmission worldwide. In the absence of a prophylactic anti-HIV vaccine, other methods of preventing infection should be implemented. Virucidal spermicides have been considered for this purpose, but their application is contraindicated by adverse effects. Anti-HIV drugs or virus-neutralizing monoclonal antibodies are expensive, suggesting that their wide use in topical chemoprophylaxis is unlikely. This emphasizes the importance of developing other methods for preventing HIV transmission. The target cells for sexual and mucosal HIV transmission include T lymphocytes, monocytes/macrophages and dendritic cells. Therefore, compounds blocking HIV-CD4 binding are expected to inhibit virus transmission. In exploring the possibility that chemical modification of food proteins might lead to compounds with anti-HIV-1 activity, we

found that bovine beta-lactoglobulin (beta-LG) modified by 3-hydroxyphthalic anhydride (3HP-beta-LG) (1) blocked at nanomolar concentrations the binding to CD4 of HIV and simian immunodeficiency virus (SIV) surface glycoproteins and monoclonal antibodies specific for the HIV binding site on CD4 and (2) inhibited infection by HIV-1, including primary virus isolates, by HIV-2 and by SIV. The inexpensive and widely available source (whey) for production of 3HP-beta-LG suggests its potential application (nonparenteral) for diminishing the frequency of HIV transmission.

I.H–11
Promising Gel Could Prevent HIV Infection in Women.

Form: Journal Article.
Author: Painter, K.
Source: USA Today. May 20, 1996.

Authors' Abstract: A vaginal gel has been shown to protect monkeys from simian immunodeficiency virus (SIV), suggesting that it could protect women from HIV. The study, led by Roberta Black of the National Institute of Allergy and Infectious Diseases, demonstrates the most promising lead yet for a chemical that women can use to protect themselves from the virus. The vaginal gel, containing a drug called PMPA, was applied to five monkeys that were then exposed to SIV, along with two other untreated monkeys. The monkeys who received the gel did not become infected, but the researchers note that further study is needed to determine whether the gel will work as well in women.

I.H–12
Modulatory Effect of N–Acetyl–L–Cysteine on the HIV–1 Multiplication in Chronically and Acutely Infected Cell Lines.

Form: Journal Article.
Author: Pani, A.; Marongiu, M. E.; La Colla, P.
Source: Antiviral Research. 22(1):31–43, September 1993.

Published Abstract: *N*–acetyl–L–cysteine (NAC) is known to antagonize the phorbol myristate acetate (PMA)– or cytokine–stimulated replication of human immunodeficiency virus type 1 (HIV–1) in latently and acutely infected monocytic and lymphocytic cell lines, and to reduce the virus multiplication in acutely infected, phytohemagglutinin (PHA)–stimulated peripheral blood mononuclear cells (PBMC). The authors here report on the modulatory effects of NAC on HIV–1 multiplication in both chronically and acutely infected lymphocytes that produce high virus levels independently from cytokine activation. In both cases, NAC doses of 0.12 and 0.25 mM decreased, whereas doses of 0.5–2 mM increased the infectious HIV–1 yield. At these concentrations, the modulatory effect of NAC on the HIV–1 multiplication paralleled that on cell proliferation, suggesting a close correlation between the two phenomena. In fact, under conditions where NAC could not modulate the cell growth, the drug also failed to modulate the HIV–1 multiplication. High NAC concentrations (4–16 mM) which were able to increase the proliferative rate of both chronically infected H9/IIIB and normal T lymphocytes, increased up to six–fold the virus multiplication in H9/IIIB cells, but were inhibitory to HIV–1 in acutely infected cells. This inhibition was due to the fact that, like dextran sulfate, NAC interfered with an early event in the virus growth cycle. The finding that high NAC doses were also capable of preventing syncytium formation in H9/IIIB and C8166 (or MT–4) cocultures further indicated an interference of the drug with events related to receptor binding.

I.H–13
Studies on the Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease and Other Genital Infections and Contraception. II. Effect In Vitro of Vaginal Contraceptive and Non–Contraceptive Preparations on *Treponema pallidum* and *Neisseria gonorrhoeae*.
Author: Singh, B.; Cutler, J. C.; Utidjian, H. M.
[See abstract IV.A–28.]

I.H–14
Maleylated–Human Serum Albumin Inhibits HIV–1 Infection In Vitro.

Form: Journal Article.
Author: Takami, M.; Sone, T.; Mizumoto, K.; Kino, K.; Tsunoo, H.
Source: Biochimica Et Biophysica Acta.

1180(2):180–186, December 10, 1992.

Published Abstract: Maleylated–human serum albumin (Mal–HSA) inhibited human immunodeficiency virus type 1 (HIV–1) infection of MT–4 cells in vitro. It was also found to inhibit the fusion between uninfected CD4+ cells (MOLT–4 clone 8 cells) and HIV–1 infected cells (MOLT–4/HIV–1) to form syncytia. To investigate the mechanism of the inhibition, a study was designed to determine whether Mal–HSA could bind to CD4+ cells. Mal–HSA could bind to both MT–4 cells and MOLT–4 clone 8 cells with high affinity (diffusion constant (K_d) = 2.0 nM and 5.8 nM, respectively). However, Mal–HSA could neither inhibit anti–CD4 antibody Leu 3a binding to MOLT–4 clone 8 cells, nor modulate the expression of CD4 molecules on the surface of the cells. Mal–HSA's binding to MOLT–4 clone 8 cells was completely inhibited by sulfated polysaccharides bearing anti–HIV activity, such as dextran sulfate, fucoidan, and carrageenan. Other HIV–1 susceptible human T–cell lines, such as MOLT–4, CEM–5, H–9, and HuT–78 cells, also have Mal–HSA binding sites showing a high affinity (Kd = 0.9 ± 0.4 nM). Mal–HSA binding proteins of MOLT–4 clone 8 cells were identified by ligand blotting as 155– and 220–kDa proteins. Unlike dextran sulfate, Mal–HSA could not inhibit reverse transcriptase activity of HIV–1. These results indicate that Mal–HSA inhibits HIV–1 infection and syncytia formation, and suggest that 155– and/or 220–kDa proteins of target cells are involved in HIV–1 adsorption and/or the membrane fusion between HIV–1 and target cells.

I.H–15
Synthesis of Protegrin–Related Peptides and Their Antibacterial and Anti–Human Immunodeficiency Virus Activity.

Form: Journal Article.
Author: Tamamura, H.; Murakami, T.; Horiuchi, S.; Sugihara, K.; Otaka, A.; Takada, W.; Ibuka, T.; Waki, M.; Yamamoto, N.; Fujii, N.
Source: Chemical & Pharmaceutical Bulletin. 43(5):853–858, May 1995.

Authors' Abstract: All disulfide analogs (types I, II, and III) of protegrin (PG)–1, an 18–residue antimicrobial peptide having two intramolecular disulfide bonds, were synthesized using regioselective disulfide bond formation. Random air–oxidation of the fully reduced PG–1 formed the type III PG–1. In addition, a type III analog containing an amidated carboxy–terminal residue was also prepared. Each analog showed significant and different antibacterial and anti–human immunodeficiency virus activity. Deletion of two disulfide bridges caused a significant decrease in activity.

I.H–16
Correlation Between Hydrophobicity and Resistance to Nonoxynol–9 and Vancomycin for Urogenital Isolates of Lactobacilli.
Author: Tomeczek, L.; Reid, G.; Cuperus, P. L.; McGroarty, J. A.; Van der Mei, H. C.; Bruce, A. W.; Khoury, A. E.; Busscher, H. J.
[See abstract I.F–8.]

I.H–17
Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl) Adenine.
Author: Tsai, C. C.; Follis, K. E.; Sabo, A.; Beck, T. W.; Grant, R. F.; Bischofberger, N.; Benveniste, R. E.; Black, R.
[See abstract I.J–18.]

I.H–18
New Antifertility Agents Active in the Rabbit Vaginal Contraception (RVC) Method.

Form: Journal Article.
Author: Williams, W. L.
Source: Contraception. 22(6):659–672, December 1980.

Published Abstract: Zinc salts in aqueous K-Y Jelly are effective vaginal contraceptives in the rabbit. The minimum effective dose is 54 to 60 mg Zn/rabbit as acetate, gluconate, or lactate. Zinc salts added to suboptimal doses of Ortho-Gynol Jelly or Delfen Cream improves the vaginal contraceptive efficacy of these products. Twenty-seven mg Zn/rabbit as lactate or acetate and 28 mg Zn/rabbit as sulfate or chloride in 0.1 to 0.5 ml of cream or jelly are effective. Gossypol is effective at a dose of 2 mg/rabbit. Although there is some rationale for their use, manganese has no antifertility effect and Valium appears to promote fertility. The rabbit vaginal contraception (RVC) method shows undesirable variation but use of sufficient animals yields logical and reliable results. Artificial insemination instead of breeding

appears to decrease variation.

Commentary: Zinc salts and gossypol have been proposed for use as vaginal microbicides.

I.H–19
Microbicidal Activity of C31g Against N. gonorrhoeae Under Conditions That Mimic The In Vivo Situation

Form: Journal Article.
Author: Malamud, D.[1], Douglas, A.[1], Rest, R.[2]
[1]Biosyn; [2]MCP/Hahnemann University, Philadelphia, PA, U.S.A.
Source: We.A.510, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: To extend our studies on the range of activities of a C31G-based microbicide to include isolates of Neisseria gonorrhoeae that are sialylated on the terminal galactose moiety of the gonococcal lipo oligosaccharide and/or grown anaerobically, and thus mimic the in vivo situation. *Methods*: C31G is a broad-spectrum agent effective against gram positive and gram negative bacteria, fungi, and enveloped viruses. It is composed of an equimolar mixture of an alkyl amine N-oxide and an alkyl N-dimethylglycine (betaine), buffered with citric acid. The chemical and physical properties of C31G can be altered by changing the length of the alkyl chains. In the present study, alkyl chain lengths of C12 vs C14/C16 were evaluated for efficacy against *N. gonorrhoeae* strain F62. Bacteria were grown under either aerobic or anaerobic conditions, and in the presence or absence of CMP-NANA to generate sialylated and non-sialylated surface lipooligosaccahrides. The efficacy of C31G was evaluated by determining the Minimum Inhibitory Concentration (MIC). *Results*: The C14/C16 form of C31G consistently showed increased efficacy as compared to the shorter alkyl chain C12 form (MIC's of 0.00032% vs .00125%). As expected, sialylated forms of *N. gonorrhoeae* demonstrated resistance to human serum bacteriocidal activity as compared with non-sialylated bacteria. On the other hand, the effects of the microbicide C31G were not diminished either by growth in anaerobic conditions, or by sialylation of the gonococci. *Conclusions*: C31G is currently under evaluation for use as a vaginal microbicide. Previous studies have shown efficacy against a variety of STD pathogens including HIV, HSV, Treponema, Chlamydia, H. ducreyi and C. albicans. In the present study, the compound has demonstrated potent in vitro activity against *N. gonorrhoeae* under conditions expected in vivo (anaerobic and sialylation of surface lipooligosaccharides). Supported by NIH grants AI 37829, AI 33505 and HD 3-3193

I.H–20
Microbicidal Gel to Prevent the Sexual Transmission of HIV.

Form: Journal Article.
Author: Bergeron, M. G.[1]; Gagne, N.[1]; Gourde, P.[1]; Perron, S.[1]; Tremblay, M.[1]; Beauchamp, D.[1]; Juhasz, J.[2]; Desormeaux, A.[1] [1]Centre de Recherche en Infectiologie, Centre Hospitalier de l'Universite Laval, Ste-Foy, Quebec, Canada; [2]Ecole de Pharmacie, Universite Laval, Ste-Foy, Quebec, Canada.
Source: We.A.512, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: To prevent the sexual transmission of HIV with the use of a microbicidal gel applied topically to the vaginal, cervical and/or ano-rectal mucosa. *Methods*: In vitro experiments have been performed to evaluate the cytotoxicity of the gel formulation in human cervical (ME-180) and colon epithelial (HT-29) cells. The efficacy of the gel to block HIV transmission has been evaluated in cell culture inserts by monitoring levels of virus particles diffusing through the gel and membrane with a p24 assay. The efficacy of the gel to prevent infection of T-lymphocytes has been determined by measuring reverse transcriptase activity in supernatant. The tolerance and toxicity of the gel preparation on the vaginal and cervical mucosa of New-Zealand rabbits has been also investigated. *Results*: The gel formulation was shown to be non-cytotoxic when applied on both human cervical and colon epithelial cells. On the other hand, results clearly demonstrated that the gel alone could act as a physical barrier which could prevent the HIV transmission. In addition, the gel delays and decreases the infection of Sup-T1 cells when compared to control without gel. Tolerance and toxicity experiments, performed in rabbits, showed that the topical application of the gel once daily for two weeks did not induce any vascularization, irritation and ulceration to the vaginal and cervical mucosa of animals. In addition, histological examinations of the different

mucosa showed no oedema, leukocyte infiltration or vascularization.
Conclusion: Entrapment of microbicides into a gel formulation and applied to the vaginal, cervical and/or ano-rectal mucosa could represent a convenient strategy to reduce the sexual transmission of HIV by acting as a physical, chemical or pharmacological barrier. Such microbicidal gels could also prolong the local microbicidal activity, eliminate local irritation and reduce systemic side effects of incorporated active agents. Taken together, these results indicate that the use of microbicidal gels could represent an innovative preventive measure which could be highly effective to reduce the transmission of HIV.

I.I. Preclinical Studies–Inert Ingredients/Delivery.

I.I–1
In Vitro Spermicidal Activity of Parabens Against Human Spermatozoa.

Form: Journal Article.
Author: Song, B. L.; Li, H. Y.; Peng, D. R.
Source: Contraception. 39(3):331–335, March 1989.

Published Abstract: Potent in vitro spermicidal activity of parabens against human spermatozoa was demonstrated in this study. The “pass” point concentration of each of the four parabens—methylparaben, ethylparaben, propylparaben, and butylparaben—at which all spermatozoa were immobilized and no immobilized spermatozoon revived after 30 minutes of incubation in phosphate–buffered glucose solution, was 6, 8, 3, and 1 mg/ml, respectively, as tested by Harris’ method. These parabens are used as food and pharmaceutical preservatives; less toxicity and fewer side effects were expected for the development of parabens as vaginal contraceptive agents.

I.J. Preclinical Studies–Methodology.

I.J–1
SIV Infection of Macaques: A Model for AIDS Vaccine Development.

Form: Journal Article.
Author: Gardner, M. B.
Source: Developments in Biological Standardization. 72259–66, 1990.

Published Abstract: The SIV macaque model is an excellent surrogate for SIV infection of humans. Genital mucosal transmission of SIV presents the opportunity for testing the effectiveness of spermicides, pharmacological agents, and vaccines in preventing the heterosexual transmission of human immunodeficiency virus (HIV). Because the incubation period is usually shorter and the disease tempo more rapid than seen with HIV infection, the endpoint for therapeutic, prophylaxis, and vaccine trials can be reached sooner in the monkey model. Initial vaccine experiments using inactivated whole SIV from the macaque (SIVmac) did not protect rhesus macaques against an intravenous or genital mucosal challenge with a moderately high dose of homologous live virus, but did appear to delay disease in the intravenously challenged group. Similarly, a modified live SIVmac immunogen also failed to protect rhesus monkeys against intravenous challenge with live virus, but did delay disease. Therefore, it appears that a strong, immediate immune response to SIVmac, whether naturally or artificially induced, can reduce the level of viremia and delay the onset of clinical. The authors believe that these inactivated whole virus and modified live virus approaches are worth pursuing further and may eventually guide researchers toward an effective vaccine for AIDS.

I.J–2
Human Vaginal Leukocytes and the Effects of Vaginal Fluid on Lymphocyte and Macrophage Defense Functions.

Form: Journal Article.
Author: Hill, J. A.; Anderson, D. J.
Source: American Journal of Obstetrics & Gynecology. 166(2):720–726, February 1992.

Published Abstract: Objectives: The purpose of this study was to quantify, characterize, and further define the role of vaginal white blood cells in defense mechanisms and human immunodeficiency virus infection. Study Design: Vaginal lavages were obtained from five healthy women throughout three menstrual cycles. Lymphocyte subpopulations, macrophages, and granulocytes were characterized and quantified by an immunohistologic technique. Vaginal lavage fluid was added to peripheral blood mononuclear cells, and effects on cell viability, lymphocyte proliferation, macrophage phagocytosis, and expression of various cell surface molecules critical to immunologic functions were assessed. Data were analyzed by Student's t test. Results: Few lymphocytes were found at any stage of the menstrual cycle; however, granulocytes and macrophages were abundant at menstruation and present at low levels through the proliferative phase. Vaginal lavage fluid collected during menses, at midcycle, and after coitus suppressed mitogen-induced lymphocyte proliferation but had no effect on surface expression of human leukocyte antigen or CD4 antigens, or on macrophage function. Likewise, low pH (less than 5.0) medium significantly inhibited lymphocyte proliferation but had no effect on macrophage phagocytosis. The spermicide nonoxynol–9 was toxic to both lymphocytes and macrophages. Conclusion: White blood cells, including lymphocytes and macrophages, are infrequently present in cervicovaginal secretions of healthy women except during menses; the vaginal environment may effect their function.

I.J–3
Infection of Rabbit T-Cell and Macrophage Lines With Human Immunodeficiency Virus.

Form: Journal Article.
Author: Kulaga, H.; Folks, T. M.; Rutledge, R.; Kindt, T. J.
Source: Proceedings of the National Academy of Sciences of the United States of America. 85(12):4455–59, June 1988.

Published Abstract: We report the successful infection of two rabbit T-cell lines and one rabbit macrophage line with human immunodeficiency virus type 1 (HIV-1). One T-cell line was a

herpes virus ateles transformant and the other was a human T-cell leukemia virus I transformant; the macrophage line was a simian virus 40 transformant. After infection with a high-titered HIV-1 stock, the rabbit cultures exhibited properties that closely mimic those of HIV-1-infected human cells. Productive infection was evident in cultures 7–14 days after infection, as shown by an increase in reverse transcriptase activity, a concomitant increase in positive cells detected by indirect immunofluorescence using serum from a patient with AIDS, and a decrease in cell viability. RNA gel blot hybridization and protein immunoblot analyses of infected cells indicated that all predicted viral transcripts and proteins were synthesized during the course of the infection. Proof that cell-free culture supernatants of the infected rabbit cell lines contained infectious virus was given by successful passage onto a susceptible human T-cell line. The ability of HIV-1 to infect transformed rabbit cell lines in vitro suggests that, with appropriate manipulation, rabbits may provide a model for infection with HIV-1.

I.J–4

Infection of Rabbits with Human Immunodeficiency Virus 1. A Small Animal Model for Acquired Immunodeficiency Syndrome.

Form: Journal Article.
Author: Kulaga, H.; Folks, T.; Rutledge, R.; Truckenmiller, M. E.; Gugel, E.; Kindt, T. J.
Source: Journal of Experimental Medicine. 169(1):321–326, January 1, 1989.

Published Abstract: Injection of rabbits with a human T–cell line infected with human immunodeficiency virus type 1 (HIV-1) caused seroconversion within 6 weeks; HIV-1 could be isolated from PBL cultures of infected rabbits. Identity of the isolated virus with HIV-1 was shown by analysis of products amplified by the polymerase chain reaction. HIV-1 infection was seen in rabbits injected with HIV-1-infected cells alone as well as in those that were first infected with HTLV-1 and subsequently with HIV-1. There were no consistent signs of disease in the rabbits infected with HIV-1 alone but HTLV-1/HIV-1-infected rabbits showed signs of illness including diarrhea and weight loss; transient neurologic impairment; and, in one animal, a rapidly progressing mammary adenocarcinoma. Examination of organs taken at necropsy from both HIV-1- and HTLV-1/HIV-1-infected animals showed splenic hyperplasia and lymphocyte infiltration of the lungs, as well as moderate damage to liver and kidney in some cases.

I.J–5

Development of Disease and Virus Recovery in Transgenic Mice Containing HIV Proviral DNA.

Form: Journal Article.
Author: Leonard, J. M.; Abramczuk, J. W.; Pezen, D. S.; Rutledge, R.; Belcher, J. H.; Hakim, F.; Shearer, G.; Lamperth, L.; Travis, W.; Fredrickson T.; et al.
Source: Science. 242(4886):1665–70, December 23, 1988.

Published Abstract: Transgenic mice containing intact copies of the human immunodeficiency virus (HIV) proviral DNA were constructed. Founder animals were not viremic for HIV and remained healthy during a 9-month observation period. After being mated with nontransgenic animals, one founder mouse (no. 13) gave rise to F1 progeny that developed a disease syndrome characterized by marked epidermal hyperplasia, lymphadenopathy, splenomegaly, pulmonary lymphoid infiltrates, growth retardation, and death by day 25 of life. Infectious HIV, indistinguishable from parental virus by immunoblot analysis, was recovered from the spleen, lymph nodes, and skin of five of five affected animals.

I.J–6

Antiviral Cytotoxic T Lymphocytes in Vaginal Mucosa of Simian Immunodeficiency Virus-Infected Rhesus Macaques.

Form: Journal Article.
Author: Lohman, B. L.; Miller, C. J.; McChesney, M. B.
Source: Journal of Immunology. 155(12):5855–60, December 15, 1995.

Published Abstract: The mucosal immune system of the female reproductive tract is of central importance for protection against sexually transmitted diseases, including HIV; however, this arm of the immune system

remains poorly understood. Antiviral cytotoxic T lymphocyte (CTL) responses have never been documented in the genital tract and the role of CTLs in this anatomic site is unknown. In this study, CD8+ intraepithelial lymphocytes (IEL) in the vaginas of six simian immunodeficiency virus (SIV)-infected female rhesus macaques were identified by immunohistochemistry to be CD2+ and TCR beta-chain+. In addition, the majority of CD8+ IEL contained TIA-1+ cytoplasmic granules that are associated with CTL activity. CD8+ T cells were isolated from the vaginal epithelium and submucosa and were amplified by limiting dilution in the presence of feeder cells. SIV p55gag and/or gp160env-specific lysis was detected in cultures of vaginal epithelial but not submucosal CD8+ T lymphocytes. Estimated SIV-specific precursor CTL frequencies were higher in the vaginal CD8+ IEL population of chronically infected monkeys than in the same cells from acutely infected monkeys or a naive control monkey. These results provide the first demonstration that antiviral CTLs are present in the vaginal epithelium, and suggest that a vaccine may be able to generate anti-HIV CTLs in the genital mucosa.

I.J–7

Genital Mucosal Transmission of Simian Immunodeficiency Virus: An Animal Model for the Heterosexual Transmission of Human Immunodeficiency Virus.

Form: Journal Article.
Author: Miller, C. J.; Alexander, N. J.; Sutjipto, S.; Lackner, A. A.; Gettie, A.; Hendrickx, A. G.; Lowenstine, L. J.; Jennings, M.; Marx, P. A.
Source: Journal of Virology. 63(10):4277–84, October 1989.

Published Abstract: This study describes the development of an animal model for the heterosexual transmission of human immunodeficiency virus (HIV) by the application of simian immunodeficiency virus (SIV) onto the genital mucosa of both mature and immature, male and female rhesus macaques. Virus preparations were infused into the vaginal vaults or the urethras (males) of the animals through a soft plastic pediatric nasogastric feeding tube. The macaques that were infected by this route (six males and nine females) developed SIV–specific antibodies. SIV was isolated from peripheral mononuclear cells of all seropositive animals. One male and one female infected by this route developed severe disease resembling acquired immunodeficiency syndrome with retroviral giant–cell pneumonia. As few as two inoculations of cell–free SIV containing 50 50% tissue culture infective doses induced persistent viremia. Cell–free virus preparations were capable of producing infection by the genital route. Much higher doses of the virus were required to transmit SIV by this route than are required for transmission by intravenous inoculation. Therefore, results indicate that the mucous membranes of the genital tract act as a barrier to SIV infection. Spermatozoa and seminal plasma were not required for the genital transmission of SIV. In rare instances, SIV was recovered from mononuclear cells in semen and vaginal secretions. The SIV–rhesus macaque model is suitable for assessing the role of cofactors in heterosexual transmission of HIV and will be useful for testing the effectiveness of spermicides, pharmacological agents, and vaccines in preventing the heterosexual transmission of HIV.

I.J–8

Langerhans Cells, Macrophages and Lymphocyte Subsets in the Cervix and Vagina of Rhesus Macaques.

Form: Journal Article.
Author: Miller, C. J.; McChesney, M.; Moore, P. F.
Source: Laboratory Investigation. 67(5):628–634, November 1992.

Published Abstract: Background: The lower reproductive tract is an important site of contact with pathogenic microorganisms and local immune responses to a variety of antigens have been reported. The purpose of this investigation was to define the morphology of the mucosa-associated lymphoid tissue in the genital tract of rhesus monkeys. Experimental Design: Monoclonal antibodies were used in an immunoperoxidase staining technique to identify immunophenotypic markers on mononuclear cells in the vaginal and cervical mucosa of 14 cycling, multiparous rhesus macaques. Results: CD1a+ Langerhans cells were present in the stratified squamous epithelium of the vagina (14 animals) and ectocervix (11 animals). Surprisingly, CD1a+ dendritic cells were also found within the columnar epithelium of the endocervix (5 animals). Moderate numbers of CD68+ macrophages were located in the submucosa of the vagina, ectocervix, and

endocervix of all the monkeys. In all of the animals, moderate numbers of CD8+ lymphocytes were present in the submucosa and squamous epithelia of the vagina and ectocervix. Variable numbers of CD20+ B cells and CD4+ lymphocytes were located in the submucosa of all the areas examined. Lymphoid nodules were present in the submucosa of vagina (14 animals) and ectocervix (4 animals), and these nodules contained macrophages, CD4+ T cells, and B cells, with fewer numbers of CD8+ T cells and Langerhans cells. Conclusions: These observations provide a morphologic basis for mucosa-associated lymphoid tissue in the female genital tract. Langerhans cells in the vaginal mucosa and endocervix may be well suited to sample antigen in the lumen of the reproductive tract, travel to the draining lymph node, present the antigen to T lymphocytes, and initiate an immune response. This pathway of antigen–presenting cell migration from the mucosa to the genital lymph node may represent the inductive arm of the mucosal immune system in the lower female reproductive tract.

I.J–9

The Cat/Feline Immunodeficiency Virus Model for Transmucosal Transmission of AIDS: Nonoxynol–9 Contraceptive Jelly Blocks Transmission by an Infected Cell Inoculum.

Author: Moench, T. R.; Whaley, K. J.; Mandrell, T. D.; Bishop, B. D.; Witt, C. J.; Cone, R. A.
[See abstract I.A.i–16.]

I.J–10

Strategies for the Inhibition of Sexual Transmission by Topical Antiviral Agents.

Form: Journal Article.
Author: O'Connor, T. J.; Jeffries, D. J.
Source: XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: A number of substances have been identified which have either a specific virucidal effect on HIV, or prevent infection of cells in vitro. Key facts are lacking in our knowledge of the efficacy and toxicity of candidate agents and this is a handicap in the planning of clinical trials. Some clinical studies suggest the possibility that topical agents may facilitate rather than inhibit HIV transmission, which may be due to damage to epithelial tissue and an increase in genital ulceration. Factors found in semen and the female genital environment may mediate the infectivity of cell–free and cell–associated HIV together with their effect on the activity of virucides. Semen and cervical secretions were assessed for their ability to inhibit HIV. Only semen was found to have any significant activity against HIV with a selectivity index (SI) of approximately 40. The effect of low pH, normally present in the female genital tract, on HIV viability was also examined by direct exposure of virus to a range of pH's and subsequent assessment for viral viability. HIV appears to be more acid stable than previously reported with no substantial reduction in infectivity occurring until pH levels are reduced below 4.5. The virucidal activity of a number of commonly used topical spermicides was assessed against cell–free and cell–associated virus using previously established and newly modified assay systems. Although nonoxynol–9 and other surfactants inactivated HIV at low concentrations, the cytotoxic effects on the cell lines used resulted in low SIs, none having an SI greater than six. Other classes of agents, such as the polysaccharides dextran sulfate and fucoidan or ionophores like gramicidin, had higher SIs (200, 200, and 50, respectively). The level of toxicity observed in some surfactants, such as nonoxynol–9, suggests that pathological effects may become apparent if these compounds are used at higher concentrations or too frequently.

I.J–11

Studies of Adhesion of Lymphocytic Cells: Implications for Sexual Transmission of Human Immunodeficiency Virus.

Form: Journal Article.
Author: Pearce–Pratt, R.; Phillips, D. M.
Source: Biology of Reproduction. 48(3):431–445, March 1993.

Published Abstract: Considerable evidence suggests that sexual transmission of human immunodeficiency virus (HIV) is mediated via mononuclear cells that can infect the epithelia of the genital tract. An in vitro model that can be used to examine the mechanism of cell–to–cell transmission of this virus is described. The authors have employed the system to identify agents that may be effective in a vaginal formulation to prevent HIV transmission via

sexual contact. They have previously shown that chronically HIV–infected mononucleocytes can infect CD4 negative epithelial monolayers in the following manner: adhesion, via multiple microvilli, of HIV–infected mononucleocyte–derived cells to epithelial monolayers activates rapid virion secretion. Virions are then shed from the attached surface of the infected lymphocyte into a partially enclosed, microvilli–laden space between the cells. The shedding results in uptake of the virus and epithelial cell infection, as demonstrated by ultrastructural examination and in vitro virological techniques. In this report, the authors present evidence from time–lapse films that HIV–infected lymphocytes adhere to the epithelium for a few minutes and then shift position to another site on the epithelium. As a result, one infected lymphocyte appears to be able to infect several cells of the epithelial monolayer sequentially. Using a fluorescence–based cell–cell adhesion assay to examine the effect of seminal fluid and a variety of chemical compounds on lymphocyte–to–epithelial adherence, the authors found that seminal fluid significantly increases the number of lymphocytes adhering to epithelia. This suggests that semen can serve as an effective medium for cell–cell transmission of HIV. On the other hand, sulfated polysaccharides and glutathione effectively inhibit cell–cell adhesion. Since the cell–cell adhesion step is critical to epithelial cell infection by HIV, these results suggest that anti–cell adhesion compounds may be effective in a vaginal formulation to reduce the probability of HIV infection.

I.J–12
HIV–1 Infection of the Trophoblast Cell Line BeWo: A Study of Virus Uptake.

Form: Journal Article.
Author: Phillips, D. M.; Tan, X.
Source: AIDS Research and Human Retroviruses. 8(9):1683–91, 1992.

Published Abstract: An in vitro model has made it possible to demonstrate transmission of human immunodeficiency virus (HIV) from infected lymphocytes to placental trophoblast cells via endocytosis. Upon addition to cultured trophoblast cells (BeWo), chronically HIV-infected lymphocytic cells (MOLT-4) adhered to the epithelial cells via a complex of newly induced microvilli. Though viruses were infrequently seen in the infected lymphocytic cell line, mature virions appeared promptly and profusely in the interstices between the interdigitating microvilli of the two cell types. Virions appeared to bud from the lymphocyte donor cells at the point of cell-to-cell contact and were rapidly taken up by the trophoblast cells via an endocytic mechanism involving coated pits, endosomes, and lysosomes. Electron microscopic observations suggest that HIV may later escape into the trophoblast cytoplasm by fusing with the endosome membrane or by lysing the lysosome membrane. Coincubation for 1 hour was sufficient to establish HIV infection in the trophoblast cell line. Four weeks after the donor lymphocytic cells were thoroughly washed out, HIV RNA was demonstrated in clusters of BeWo cells by in situ hybridization, and p24 antigen was localized with immunocytochemistry. Soluble CD4 did not block infection, as measured by p24 enzyme–linked immunosorbent assay (ELISA). The HIV infection was productive and chronic, as demonstrated by cocultivating the BeWo cells with indicator lymphocytes 4 weeks after the initial infection. This study demonstrating a mechanism of HIV transmission expands on previous observations that trophoblast cell lines lacking the CD4 viral receptor can nevertheless be infected by HIV and can support productive infection.

I.J–13
Mechanisms of Sexual Transmission of HIV: Does HIV Infect Intact Epithelia?

Form: Journal Article.
Author: Phillips, D. M.; Zacharopoulos, V. R.; Tan, X.; Pearce–Pratt, R.
Source: Trends in Microbiology. 2(11):454–458, November 1994.

Published Abstract: The prevailing view of sexual transmission of human immunodeficiency virus (HIV) has been that the virus enters the body through lesions in the epithelium of the genital tract. The authors propose that transmission of HIV can occur via the infection of intact epithelial cells and that it is mediated by HIV-infected mononuclear cells in genital tract secretions.

I.J–14
A Monocyte-Derived Factor Interferes With

Detection of Reverse Transcriptase in HIV-1 Infection.

Form: Journal Article.
Author: Recker, D. P.; Kulaga, H.; Dorsett, D.; Folks, T.; Kindt, T. J.
Source: AIDS Research & Human Retroviruses. 7(1):73–81, January 1991.

Published Abstract: Culture supernatants from the rabbit macrophage cell line 6083 infected with a retrovirus, human immunodeficiency virus type 1 (HIV-1), were negative for reverse transcriptase (RT) expression although the line was shown to be productively infected by all other criteria tested. Supernatants from uninfected cultures of 6083, the human monocyte line U937, and from freshly isolated peripheral human monocytes, were found to contain a monocyte-derived inhibitory factor (MDIF) which interferes with a standard assay for RT. MDIF is a heat-labile activity of approximately of 40 kD. Both substrates and products of the RT assay are degraded by MDIF which is not affected by reduction and alkylation of disulfide bonds. MDIF is inhibited by the addition of a particular thioated oligonucleotide (S-dG30) to the reaction mixture; this addition also inhibits RT. The optimum method to minimize MDIF interference in the RT assay is by addition of ethylene glycol bis-(beta-aminoethyl ether)N,N,N',N'-tetraacetic acid (EGTA); MDIF requires divalent cations for activity and has a strong preference for calcium which is preferentially chelated by EGTA. The potential presence of this inhibitory activity should be considered when using RT levels as a measure of retroviral infection.

I.J–15
Trichomonacidal Activity of Human Polymorphonuclear Neutrophils Killing by Disruption and Fragmentation.

Form: Journal Article.
Author: Rein, M. F.; Sullivan, J. A.; Mandell, G. L.
Source: Journal of Infectious Diseases. 142(4):575–585, October 1980.

Published Abstract: Polymorphonuclear neutrophils (PMNs) were shown to kill *Trichomonas vaginalis* in vitro; 10^2–10^3 trichomonads were incubated with 3 x 10^6 PMNs on tissue culture plates, and surviving organisms were enumerated in pour plates. After 60 minutes of aerobic incubation at 37EC, 100% (±0) of the trichomonads had been killed, and nitroblue tetrazolium was reduced at the interface between the PMNs and trichomonads. The importance of oxidative microbicidal systems was confirmed by the observations that only 12% (±12%) of trichomonads were killed under anaerobic conditions, and that aerobic killing was eliminated by the addition of catalase or superoxide dismutase. PMNs killed trichomonads in fresh or absorbed serum but not in bovine serum albumin, in heat–inactivated serum, or in the presence of 1 mM trypan blue; this finding suggested a role for alternative pathway activation of complement. Phase–contrast cinemicrography and electron microscopy revealed the pursuit and surrounding of individual trichomonads by groups of PMNs that were able to fragment the large protozoa and to phagocytize the pieces.

I.J–16
Cellular Targets of Infection and Route of Viral Dissemination After an Intravaginal Inoculation of Simian Immunodeficiency Virus Into Rhesus Macaques.

Form: Journal Article.
Author: Spira, A. I.; Marx, P. A.; Patterson, B. K.; Mahoney, J.; Koup, R. A.; Wolinsky, S. M.; Ho, D. D.
Source: Journal of Experimental Medicine. 183(1):215–25, January 1, 1996.

Published Abstract: We used the simian immunodeficiency virus rhesus macaque (SIVmac) model to study events that underlie sexual transmission of human immunodeficiency virus type 1 (HIV-1). Four female rhesus macaques were inoculated intravaginally with SIVmac251, and then killed 2, 5, 7, and 9 days later. A technique that detected polymerase chain reaction-amplified SIV in situ showed that the first cellular targets for SIV were in the lamina propria of the cervicovaginal mucosa, immediately subjacent to the epithelium. Phenotypic and localization studies demonstrated that many of the infected cells were likely to be dendritic cells. Within 2 days of inoculation, infected cells were identified in the paracortex and subcapsular sinus of the draining internal iliac lymph nodes. Subsequently, systemic dissemination of SIV was rapid, since culturable virus was detectable

in the blood by day 5. From these results, we present a model for mucosal transmission of SIV and HIV-1.

I.J–17
Evaluation of the Amount of Nonoxynol Available in Condoms for the Inhibition of HIV Using a Method Based on HPLC.
Author: Trap, R.; Trap, B.; Petersen, C. S.
[See abstract I.A.i–29.]

I.J–18
Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl) Adenine.

Form: Journal Article.
Author: Tsai, C. C.; Follis, K. E.; Sabo, A.; Beck, T. W.; Grant, R. F.; Bischofberger, N.; Benveniste, R. E.; Black, R.
Source: Science. 270(5239):1197–99, November 17, 1995.

Published Abstract: The efficacy of pre- and postexposure treatment with the antiviral compound (R)-9-(2-phosphonylmethoxypropyl) adenine (PMPA) was tested against simian immunodeficiency virus (SIV) in macaques as a model for human immunodeficiency virus (HIV). PMPA was administered subcutaneously once daily, beginning either 48 hours before, 4 hours after, or 24 hours after virus inoculation. Treatment continued for 4 weeks and the virologic, immunologic, and clinical status of the macaques was monitored for up to 56 weeks. PMPA prevented SIV infection in all macaques without toxicity, whereas all control macaques became infected. These results suggest a potential role for PMPA prophylaxis against early HIV infection in cases of known exposure.

Commentary: PMPA has been proposed as a potential vaginal microbicide.

II.A. Clinical Studies–Methodology.

II.A–1
Cellular and Soluble Factors in Semen and the Vaginal Environment That May Influence the Heterosexual Transmission of HIV Type 1.

Form: Book Chapter.
Author: Anderson, D. J.; Hill, J. A.
Source: IN: Vaginitis and Vaginosis. Horowitz, B. J.; Per–Anders, M., eds. New York: Wiley–Liss., pp. 69–76, 1991.

Published Abstract: None.
Annotators' Abstract: The authors review current information on the immunologic microenvironment of human semen and cervicovaginal fluid, focusing on lymphocyte and macrophage populations, with particular regard to mechanisms of transmission of human immunodeficiency virus type 1 (HIV–1). They describe the ways in which male and female reproductive tissues provide a unique environment for HIV–1 infection, outlining how immunosuppressive factors found in these tissues may locally suppress cellular and humoral defense mechanisms directed against HIV–1 infected cells and free viral particles. The authors also point out that genital tract inflammation occurs frequently in response to subclinical and clinical infections and may be a cofactor in the sexual transmission of HIV–1. They conclude that to understand fully the dynamics of the sexual transmission of HIV–1, a working knowledge of the specialized environment and infections of the reproductive tract is needed.

II.A–2
Effectiveness of Condoms for Prevention of HIV Infections.
Author: Judson, F. N.
[See abstract IV.A–18.]

II.A–3
Design of Clinical Studies of Spermicides for Prophylaxis Against Sexually Transmitted Diseases.

Form: Book Chapter.
Author: Foldesy, R. G.; Farr, M. G.; Thompson, D. C.; Catotti, D. N.
Source: IN: Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989. Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M., eds. New York: Wiley–Liss., pp. 291–301, 1990.

Published Abstract: None.
Annotators' Abstract: The authors discuss the experience of Family Health International in carrying out four clinical trials of spermicides and other prophylactic products in a population of women in Columbia at high risk for sexually transmitted diseases (STDs). They focus on logistical challenges, adherence to product use, and protocol development and approval.

II.A–4
Human Vaginal Leukocytes and the Effects of Vaginal Fluid on Lymphocyte and Macrophage Defense Functions.

Form: Journal Article.
Author: Hill, J. A.; Anderson, D. J.
Source: American Journal of Obstetrics & Gynecology. 166(2):720–726, February 1992.

Published Abstract: Objectives: The purpose of this study was to quantify, characterize, and further define the role of vaginal white blood cells in defense mechanisms and human immunodeficiency virus infection. Study design: Vaginal lavages were obtained from five healthy women throughout three menstrual cycles. Lymphocyte subpopulations, macrophages, and granulocytes were characterized and quantified by an immunohistologic technique. Vaginal lavage fluid was added to peripheral blood mononuclear cells, and effects on cell viability, lymphocyte proliferation, macrophage phagocytosis, and expression of various cell surface molecules critical to immunologic functions were assessed. Data were analyzed by Student's t test. Results: Few lymphocytes were found at any stage of the menstrual cycle; however, granulocytes and macrophages were abundant at menstruation and present at low levels through the proliferative phase. Vaginal lavage fluid collected during menses, at midcycle, and after coitus suppressed mitogen-induced lymphocyte proliferation but

had no effect on surface expression of human leukocyte antigen or CD4 antigens or on macrophage function. Likewise, low pH (less than 5.0) medium significantly inhibited lymphocyte proliferation but had no effect on macrophage phagocytosis. The spermicide nonoxynol–9 was toxic to both lymphocytes and macrophages. Conclusion: White blood cells, including lymphocytes and macrophages, are infrequently present in cervicovaginal secretions of healthy women except during menses; the vaginal environment may affect their function.

II.A–5
Quantitative Analysis of Nonoxynol–9 in Blood.

Form: Journal Article.
Author: Yang, J. T.; Zhao, Z. W.
Source: Contraception 43(2):161–166, February 1991.

Published Abstract: At present there is little data on the level of nonoxynol–9 in blood. Using routine methods, the rate of recovery for nonoxynol–9 in blood has been confirmed to be very low. A method determining nonoxynol–9 levels in blood and urine is still needed. A method of determining nonoxynol–9, a nonionic surfactant spermicide, in blood is presented here. The analytical procedure is a simple and convenient method. Using high–performance liquid chromatography (HPLC), ultraviolet (UV) detector, octyldecyl silane (ODS) reversed–phase column, methanol–water mobile phase, NaCl salting–out, and two extractions with benzene, a rate of recovery for nonoxynol–9 of 93 ±4% has been obtained.

II.A–6
HIV–1 Detection in Endocervical Swabs and Mode of HIV–1 Infection.

Form: Journal, Letter.
Author: Zorr, B.; Schafer, A. P.; Dilger, I.; Habermehl, K. O.; Kosh, M.
Source: Lancet. 343(8901):852, April 2, 1994.

Published Abstract: None.
Annotators' Abstract: Polymerase chain reaction (PCR) was used to detect HIV–1–specific DNA in endocervical swabs from 25 female patients infected with HIV–1. A control group of 33 patients without HIV–1 infection tested negative by PCR. HIV–1–specific DNA was found in 12 of 25 endocervical swabs. The HIV–1 infected patients were grouped according to assumed route of infection: 12 via sexual and 13 via intravenous transmission. Of the patients whose HIV transmission was sexual, 75% showed HIV–1 DNA in the endocervical swabs. The detection rate for patients whose HIV–1 transmission was intravenous was significantly lower (23%, P = 0.003). No relation between CD4 cell numbers and the HIV–1 detection rate was found. The authors speculate that if the detected HIV–1–specific DNA is infectious material, it may help explain the differences in the risk of transmission of HIV–1 infection in various patient populations.

II.B.*i.* Clinical Studies of Safety/Adverse Effects–Nonoxynol–9.

II.B.i–1
Contraceptive Film Acceptability Study: Mexico.
Author: Alvarado, G.
[See abstract III.A–2.]

II.B.i–2
The Prevalence of HIV Infection Among Women Attending a Sexually Transmitted Disease Clinic in Birmingham, Alabama.

Form: Journal Article.
Author: Austin, H.; Louv, W. C.; Alexander, W. J.; Cheeks, J.; Perlman, J.; Weiss, S. H.
Source: AIDS. 3(5):322–323, 1989.

Published Abstract: None.
Annotators' Abstract: From 1986 through 1987, 300 women recruited from a previous clinical trial of nonoxynol–9 were interviewed at a sexually transmitted disease (STD) clinic in Birmingham. Anal intercourse was reported by 13%. Despite previous intensive counseling, only 6% reported regularly using condoms, and only 2.7% regularly used spermicides. One woman was seropositive for human immunodeficiency virus (HIV). The survey also indicated that 3.0% had a history of intravenous drug use. The average levels of sexual activity had not changed since the clinical trial. These results underline the importance of consistent and effective risk–reduction counseling for STD patients.

II.B.i–3
Adverse Effects of Nonoxynol–9.

Form: Journal Article, Letter.
Author: Berer, M.
Source: Lancet. 340(8819):615–616, September 5, 1992.

Published Abstract: None.
Annotators' Abstract: This letter was written in response to an editorial that concluded that the effects of cumulative vaginal doses of nonoxynol–9 for Thai sex workers were mitigated by the frequent use of douches. The author states that douching has not been recommended because of potential adverse effects and noted that the Thai study evaluated only short–term effects. The author concludes that the role of spermicides in aggravating existing reproductive tract infections is not known.

II.B.i–4
Comment: The Use of Spermicide Containing Nonoxynol–9 in the Prevention of HIV Infection.
Author: Bird, K. D.
[See abstract II.C.ii.a–2.]

II.B.i–5
Nonoxynol–9 and the Reduction of HIV Transmission in Women (reply to Gollub and Stein).

Form: Journal Article.
Author: Bird, K.
Source: AIDS. 6(6):601, June 1992.

Published Abstract: None.
Annotator's Abstract: The author responds to a letter from Gollub and Stein, who criticized findings on the safety and toxicity of nonoxynol–9, reported in a review article on nonoxynol–9.

II.B.i–6
Vaginal Spermicides, Chromosomal Abnormalities and Limb Reduction Defects.

Form: Journal Article.
Author: Cordero, J. F.; Layde, P. M.
Source: Family Planning Perspectives. 15(1):16–8, January–February 1983.

Published Abstract: Each year, 300,000–600,000 U.S. women become pregnant while using vaginal spermicides. Two recent reports hypothesized that offspring from these pregnancies are at increased risk of certain birth defects, particularly limb reduction defects and such chromosomal abnormalities as Down's syndrome. In a case-control analysis of data from the Metropolitan Atlanta Congenital Defects Program (MACDP), we studied the teratogenicity of spermicides by comparing their use around the time of conception by mothers of infants with chromosomal abnormalities and

limb reduction defects to their use by mothers of infants with birth defects that have not been linked to spermicides. The results do not support the hypothesis that spermicides are teratogenic. For infants whose mothers used spermicides at the time of conception, the relative risk of having Down's syndrome was 1.2; that for other chromosomal abnormalities was also 1.2. The relative risk of limb reduction defects among infants exposed to spermicides in the first trimester was 1.0. None of these risks is statistically significant.

II.B.i–7

Association Between Use of Spermicide-Coated Condoms and *Escherichia coli* Urinary Tract Infection in Young Women.

Form: Journal Article.
Author: Fihn, S. D.; Boyko, E. J.; Norman, E. H.; Chen, C. L.; Grafton, J. R.; Hunt, M.; Yarbro, P.; Scholes, D.; Stergachis, A.
Source: Am J Epidemiology. 144:512–520, 1996.

Abstract: Diaphragm/spermicide use increases the risk of urinary tract infections (UTIs). To determine whether spermicide coated condoms are also associated with an increased risk for UTIs, the authors conducted a case-control study at a large health maintenance organization in Seattle, Washington. Cases were sexually active young women with acute UTIs caused by *Escherichia coli*, identified from computerized laboratory files during 1990–1993. Age matched controls were randomly selected from the enrollment files of the plan. Of 1,904 eligible women, 604 cases and 629 controls (65%) were interviewed. During the previous year, 40% of the cases and 31% of the controls had been exposed to any type of condom. The unadjusted odds ratio for UTI cases increased with frequency of condom exposure from .91 (95% confidence interval (CI), 0.65–1.28) for weekly or less during the previous month to 2.11 (95% CI, 1.37–3.26) for more than once weekly. Exposure to spermicide-coated condoms conferred a higher risk for UTI, with odds ratios ranging from 1.09 (95% CI, 0.58–2.05) for use weekly or less to 3.05 (95% CI, 1.47–6.35) for use more than once weekly. In multivariate analyses, intercourse frequency (odds ratio (OR) = 1.14 per weekly episode), history of UTIs (OR = 2.64), and frequency of spermicide-coated condom exposures (OR = 3.334) for more than once weekly and 5.65 for use more than twice weekly) were independent predictors of UTIs. Spermicide-coated condoms were responsible for 42% of the UTIs among women who were exposed to these products.

II.B.i–8

Allergic Contact Dermatitis to Nonoxynol–9 in a Condom.

Form: News Article.
Author: Fisher, A. A.
Source: Cutis. 53(3):110–111, March 1994.

Published Abstract: None.
Annotators' Abstract: This article presents a case report of allergic contact dermatitis in a 32–year–old man after he used condoms containing nonoxynol–9. The source of the reaction was confirmed to be nonoxynol–9 by the subject's positive reaction to a 2% aqueous solution of the compound. Results of the same test in three control subjects were negative. The subject's use of a rubber condom free of nonoxynol–9 did not elicit a reaction. Reports of contact dermatitis in response to nonoxynols in waterless hand cleansers and in detergents were located. The article concludes with a discussion of nonoxynol–9–containing spermicides, and the detergent action and cytotoxicity of nonoxynol–9.

II.B.i–9

Vaginal Spermicides and Outcome of Pregnancy: Findings in a Large Cohort Study.

Form: Journal Article.
Author: Huggins, G.; Vessey, M.; Flavel, R.; Yeates, D.; McPherson, K.
Source: Contraception. 25(3):219–230, March 1982.

Published Abstract: By the end of 1980, 5,729 singleton planned pregnancies; 1,552 singleton unplanned pregnancies; and 81 multiple pregnancies had been observed among the 17,032 participants in the Oxford-Family Planning Association contraceptive study. The outcome of these pregnancies was investigated in relation to the use of vaginal spermicides. There was some suggestion that spermicide use might have a small adverse effect on the risk of

congenital malformations, especially among infants conceived as a result of contraceptive failure. There was not, however, any evidence of any other adverse effect of spermicide use. In particular, the results provide strong evidence against the hypothesis that spermicide use has any appreciable effect on the risk of spontaneous abortion.

II.B.i–10
The In Vivo Effects of Nonoxynol–9 Contraception on Vaginal Microbial Flora and Colonization With *Escherichia coli*.
Author: Jones, B. M.; Eley, A.
[See abstract I.F–3.]

II.B.i–11
Comparison of the Influence of Spermicidal and Nonspermicidal Contraception on Bacterial Vaginosis, Candidal Infection and Inflammation of the Vagina—A Preliminary Study.
Author: Jones, B. M.; Eley, A.; Hicks, D. A.; Patel, R.; Wordsworth, J. M.
[See abstract II.C.iii.a–1.]

II.B.i–12
Efficacy of Nonoxynol–9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes.
Author: Kreiss, J.; Ngugi, E.; Holmes, K.; Ndinya–Achola, J.; Waiyaki, P.; Roberts, P. L.; Ruminjo, I.; Sajabi R.; Kimata, J.; Fleming, T. R.; et al.
[See abstract II.C.i.a–7.]

II.B.i–13
Maternal Exposure to Spermicides in Relation to Certain Birth Defects.

Form: Journal Article.
Author: Louik, C.; Mitchell, A. A.; Werler, M. M.; Hanson, J. W.; Shapiro, S.
Source: New England Journal of Medicine. 317(8):474–478, August 20, 1987.

Published Abstract: Several studies have found no increase in the overall frequency of birth defects in association with the use of spermicides, but the possibility of an increase in specific defects remains. We evaluated this possibility in a large case-control study. Infants with certain malformations (265 with Down's syndrome, 396 with hypospadias, 146 with limb reduction defects, 116 with neoplasms, and 215 with neural-tube defects) were compared with 3,442 control infants with a wide variety of other defects. Exposure to spermicides was assessed for three periods: use during the periconceptional period (one month before through one month after the last menstrual period), use during the first trimester (the first four lunar months of pregnancy), and any use during the lifetime. For the five groups of cases and for each interval, the odds ratios were close to 1.0 (range, 0.7 to 1.3); the upper 95 percent confidence bounds were 2.2 or lower. Risks did not increase with the duration of exposure. When each of the active ingredients in currently available spermicides was considered separately, no differences in odds ratios were apparent between the types of spermicides. With the possible exception of a subgroup of cases (limb reduction defects of unknown cause), these results suggest that risks for the five specific birth defects evaluated are not increased by exposure to spermicides.

II.B.i–14
Preliminary Results, Serum Chemistry Values Before and After the Intravaginal Administration of 5% Nonoxynol-9 Cream.
Author: Malyk, B.
[See abstract II.D.i–3.]

II.B.i–15
Inappropriate Lubricant Use With Condoms by Homosexual Men.

Form: Journal Article.
Author: Martin, D. J.
Source: Public Health Reports. 107(4):468–473, July–August 1992.

Authors' Abstract: Use of condoms has been advocated as an important method of reducing the risk of human immunodeficiency virus (HIV) transmission among high–risk groups such as homosexual and bisexual men, prostitutes, intravenous drug users, adolescents, and hemophiliacs. Despite risk–reduction education campaigns directed to gay men since the early 1980s, evidence shows continued deficits in condom–use skills and knowledge among gay men. Because most failures in the use of condoms are attributed to errors in use,

increasing knowledge and skills in condom use is important in preventing HIV infection. Two groups of homosexual and bisexual men were sampled, those entering a risk–reduction education program and participants in a Gay Pride event. They were surveyed on their current sex practices and their efforts to reduce their risk of HIV infection. They were asked about their numbers of sex partners, specific sexual behaviors, use of condoms, types of condoms used, and lubricants used for genital–anal sex. The characteristics of those surveyed were similar to those of respondents in other studies of risk reduction among gay men. The use of an oil–based lubricant with condoms has been shown to weaken latex and to increase the likelihood of condom breakage, which use of water–based lubricants does not. Among respondents who reported having genital–anal sex, 60 percent reported use of an oil–based lubricant with a condom at least once during the year before the survey. Gay men in sexually exclusive relationships engaged in less consistent use of condoms for receptive genital–anal sex than did single gay men.

II.B.i–16
Severe Chemical Cystitis From the Transurethral Intravesical Insertion of a Vaginal Contraceptive Suppository: A Report of 3 Cases and Proposed Method of Management.

Form: Journal Article.
Author: Mayersak, J. S.; Viviano, C. J.
Source: Journal of Urology. 149(4):835–837, April 1993.

Published Abstract: The authors report three case studies of patients who sustained severe chemical cystitis from the inadvertent insertion of a nonoxynol–9–containing vaginal contraceptive suppository into the bladder. A suggested treatment schedule is presented and the toxicity of nonoxynol–9 is discussed.

II.B.i–17
The Effects of Frequent Nonoxynol–9 Use on the Vaginal and Cervical Mucosa.

Form: Journal Article.
Author: Niruthisard, S.; Roddy, R. E.; Chutivongse, S.
Source: Sexually Transmitted Diseases. 18(3):176–179, July–September 1991.

Published Abstract: The authors conducted a single–dose phase I local toxicity study of the effects of frequent insertion of nonoxynol–9 on the lower genital tract to determine whether a phase II dose–ranging study is warranted. Fourteen women used 150 mg of nonoxynol–9 cumulatively 4 times day for 14 days. Epithelial disruption of the cervix and vagina, the main outcome of interest, occurred in 43% of women on this high–frequency use schedule (95% confidence interval (CI) 18%–71%). None of the women experienced symptoms that prompted them to discontinue the study. This preliminary study indicates that a phase II study to examine the local toxicity of different use schedules is needed to provide further safety information about the use of nonoxynol–9.

II.B.i–18
Use of Nonoxynol–9.

Form: Journal Article, Letter.
Author: O'Farrell, N.; Barlow, D.
Source: Lancet. 340(8812):179, July 18, 1992.

Published Abstract: None.
Annotators' Abstract: This letter addresses a report by Dr. Niruthisard and colleagues stating that nonoxynol–9 reduces the rate of gonococcal and chlamydial infections in high–risk women (see II.C.i.a–10). The authors suggest that previously reported toxic and irritative effects of nonoxynol–9 may promote the transmission of human immunodeficiency virus type 1 (HIV–1) in populations with a high frequency of gonococcal and chlamydial infections. They also point out that condoms alone, used correctly and consistently, reduce the frequency of gonorrhea without adverse effects. They conclude that before recommending nonoxynol–9 to limit the spread of sexually transmitted diseases, further studies are needed to determine the risk of HIV–1 transmission associated with the use of nonoxynol–9.

II.B.i–19
Comparison of Spermicides on Vulvar, Vaginal and Cervical Mucosa.

Form: Journal Article.
Author: Poindexter, A. N.; Levine, H.;

Sangihaghpeykar, H.; Frank, M. L.; Grear, A.; Reeves K. O.
Source: Contraception. 53(3):147–153, March 1996.

Published Abstract: The objective of this study was to compare the tolerability of Advantage 24® to two other spermicides containing nonoxynol-9 (N-9). These spermicides were Today® Sponge (the Sponge) and Conceptrol®. In order to examine the incidence of complaints and the clinical observation of vaginal ulceration and irritation of the three spermicides, a randomized, open–label, three–period cross-over trial was conducted. Thirty-three women, ages 18–45, with a normal vaginal environment based on physical exam, Pap smear, vaginal wet prep, colposcopy, and serum N-9 were randomized into four treatment groups. Each treatment was for 7 consecutive days with a 21-day washout. Data obtained were studied by one-way analysis of variance, chi-square, and Kruskal-Wallis tests. No vulvar or vaginal abnormality was observed from either spermicide. Subjects had fewer and less severe cervical lesions by colposcopy during treatment with Advantage 24 than with Conceptrol® or the Sponge ($p<0.01$). Comparison of the incidence of abnormal gynecological findings, serum N-9 levels, and the incidence of adverse events before and after treatment with the three study drugs indicate that most subjects had normal examinations pre- and post-treatment. Pap smear and colposcopy changes from normal to abnormal accounted for about 50% of all gynecological findings during the Conceptrol® and Sponge treatments, but less than 20% during treatment with Advantage 24. All serum N-9 levels were below the level of detection (<1.9 mu g/ml). Advantage 24 is better tolerated than Conceptrol® or the Sponge. Furthermore, the cervical mucosa appears to be less resilient to spermicides than vulvo-vaginal mucosa.

II.B.i–20
The Toxicity and Local Effects of the Spermicide Nonoxynol–9.

Form: Journal Article, Letter.
Author: Rekart, M. L.
Source: Journal of Acquired Immune Deficiency Syndromes. 5(4):425–427, 1992.

Published Abstract: None.
Annotators' Abstract: A questionnaire was administered to 71 street–recruited commercial sex workers (CSWs) in British Columbia. All but 1 of the 64 female and 7 male CSWs had used latex condoms lubricated with nonoxynol–9 for anal, vaginal, or oral sex. Of the 60 females who had used these condoms for vaginal intercourse, 33 (55%) reported one or more adverse, local vaginal reactions, including vaginal irritation or burning (53.3%) and an increase in yeast infections (8.3%). Of the 48 CSWs who used the condoms for oral sex, 45 (93.8%) had had one or more adverse oral reactions. Because of these experiences, 44 CSWs reported that they stopped using latex condoms lubricated with nonoxynol–9. The authors conclude that CSWs' repeated exposure to nonoxynol–9–lubricated latex condoms may cause vaginal irritation and inflammation that could be directly related to dosage of and frequency of exposure to nonoxynol–9.

II.B.i–21
A Dosing Study of Nonoxynol–9 and Genital Irritation.

Form: Journal Article.
Author: Roddy, R. E.; Cordero, M.; Cordero, C.; Fortney, J. A.
Source: International Journal of STDs and AIDS. 4(3):165–170, May–June 1993.

Published Abstract: The objective of the study was to assess the signs and symptoms of genital irritation produced by different frequencies of nonoxynol–9 use. Thirty–five women were randomized to five groups and used a nonoxynol–9 vaginal suppository for 2 weeks: Group 1, once every other day; Group 2, once a day; Group 3, twice a day; Group 4, four times a day; and Group 5, placebo four times a day. The women were examined at admission, at 1 week, and at 2 weeks with a colposcope for erythema and epithelial disruption, and were interviewed about vaginal itching and burning. The rates of reported symptoms for nonoxynol–9 users were not significantly different from that of placebo users. The rate of epithelial disruption for women using nonoxynol–9 every other day was essentially the same as that of women using a placebo. The rates of epithelial disruption for women using nonoxynol–9 once a day and twice a day were two and a half times greater than that of placebo users. The rate of epithelial disruption for women using nonoxynol–9 four times a day was five times greater than that of placebo users.

Genital irritation was located primarily on the vagina or cervix, and vulvitis was not a significant problem. Women who use nonoxynol–9 products infrequently may not experience an increase in genital irritation. Women who use nonoxynol–9 frequently may experience an increase in epithelial disruption.

II.B.i–22
Spermicide Use and Down's Syndrome.

Form: Journal Article.
Author: Rothman, K. J.
Source: American Journal of Public Health. 72(4):399–401, April 1982.

Published Abstract: A connection has been suggested between use of vaginal spermicides and the occurrence of Down's syndrome among offspring born to women who used these contraceptive agents. This hypothesis was evaluated with data from a case–control study of congenital heart disease, which included among the subjects 16 infants with Down's syndrome. The estimated prevalence ratio of the proportion of Down's syndrome births among reported spermicide users to the proportion in nonusers was 3.6 (90% confidence interval, 1.2–9.0), thus providing a tentative confirmation of the hypothesis.

II.B.i–23
Spermicides for Controlling the Spread of HIV.

Form: Journal Article, Letter.
Author: Voeller, B.
Source: AIDS. 6(3):341–342, March 1992.

Published Abstract: None.
Annotators' Abstract: The author is responding to Bird's article (see II.C.ii.a–2) that urged caution in the use of spermicides for HIV prevention because of nonoxynol–9–related irritation. It is not known whether the vehicle, brand of condom, or the concentration of nonoxynol–9 was the cause of this irritation. The author reports his own observations of 50 homosexual men who used a 1% nonoxynol–9 lubricant rectally for months or years. Only men who used higher concentrations of nonoxynol–9 complained of rectal irritation.

II.B.i–24
Lack of Association Between Spermicide Use and Trisomy.

Form: Journal Article.
Author: Warburton, D.; Neugut, R. H.; Lustenberger, A.; Nicholas, A. G.; Kline, J.
Source: New England Journal of Medicine. 317(8):478–482, August 20, 1987.

Published Abstract: It has been suggested that the maternal use of spermicidal contraceptives increases the frequency of certain congenital anomalies, including trisomy, but this issue is in dispute. This controversy led us to examine whether the use of spermicidal contraceptives is associated with an increased risk of fetal trisomy. A questionnaire concerning contraceptive use was completed by 13,729 women who were undergoing prenatal fetal chromosome studies but were as yet unaware of the results. Most women were at increased risk of having a trisomic fetus because of their advanced age. Of 154 fetuses with trisomy, 98 had trisomy 21. For each woman (case) with an affected fetus, four controls were selected from among women with chromosomally normal fetuses, matched for maternal age and medical center. Cases and controls were compared by matched-sample maximum-likelihood logistic regression, to examine the association between fetal trisomy and four measures of spermicide use: periconceptional use, timing of last use, duration of last use, and total lifetime use. No evidence was found for an association, either when all types of trisomy were combined or when trisomy 21 alone was considered. All point estimates of odds ratios relating spermicidal exposure to trisomy were approximately 1, and an effect greater than a twofold increase was excluded with 95 percent confidence in the combined-trisomy group for all measures of spermicide use.

II.B.i–25
Nonoxynol-9 in Lubricated Condoms: Results of a Study in Female Prostitutes.

Form: Journal Article.
Author: Ward, H.; De La Court, A.; Kitchen, V.
Source: STD. 413–414, September–October 1996.

Abstract: Background and Objectives: Debate continues on the efficacy and safety of

intravaginal nonoxynol-9 for the prevention of horizontal transmission of human immunodeficiency virus and other sexually transmitted diseases. Little attention has been paid to the effects of nonoxynol-9 contained in the lubricant of many condoms. Goal: To assess the tolerability of different levels of nonoxynol-9 in condom lubricants. Study Design: Pilot, randomized, controlled study using female prostitutes. Results: There was no association between dose of nonoxynol-9 and reported symptoms or signs of genital tract inflammation; an increased dose of nonoxynol-9 was associated with increased numbers of polymorphonuclear leukocytes on a vaginal wall smear. Conclusions: There is no recognized simple method of defining inflammation in the female genital tract. Future studies of the effect of low-dose nonoxynol-9 on the female genital tract require highly controlled exposures, plus colposcopy with or without vaginal biopsy to define inflammation.

II.B.i–26
Nonoxynol–9 Use, Genital Ulcers, and HIV Infection in a Cohort of Sex Workers.

Form: Journal Article.
Author: Weir, S. S.; Roddy, R. E.; Zekeng, L.; Feldblum, P. J.
Source: Genitourinary Medicine. 71(2):78–81, April 1995.

Published Abstract: Objective: The authors measured the associations between use of nonoxynol–9 and the incidence of genital ulcers and incident ulcers and human immunodeficiency virus (HIV) seroconversion. Methods: In this study, 273 female sex workers used condoms and 100–mg nonoxynol–9 suppositories and recorded sexual activity on coital logs. Genital ulcers were diagnosed clinically at monthly clinic visits. HIV infection was diagnosed by enzyme–linked immunosorbent assay (ELISA) and Western blot among women who had at least six months of follow–up. The authors calculated ulcer incidence rates by level of nonoxynol–9 use. A nested, matched, case–control analysis assessed the effect of ulcers on HIV acquisition. Results: More frequent nonoxynol–9 use was not associated with genital ulcers and may have been protective against the lesions. Ulceration was not a strong risk factor for HIV acquisition in this study (odds ratio 1.1; 95% confidence internal 0.3–3.5). Conclusion: Frequent use of nonoxynol–9 can cause genital irritation and ulceration. Ulcers, in turn, may be risk factors for HIV acquisition. This study, however, did not find an association between nonoxynol–9 use and ulcers, nor between ulcers and HIV. There is probably a threshold of nonoxynol–9 use frequency or a dose below which the risk of ulceration is minimal. Ulcers due to infectious causes may have been prevented by nonoxynol–9 use in this cohort.

II.B.i–27
[Real and False Risk of Local Contraception: Spermicides and the Diaphragm.] [French.]
Author: Zufferey, M. M.
[See abstract IV.A–35.]

II.B.*ii.* Clinical Studies of Safety/Adverse Effects–Other Spermicides.

II.B.ii–1
A Clinical Trial of Neo Sampoon Vaginal Contraceptive Tablets.

Form: Journal Article.
Author: Begum, S. F.; Liao, W. C.; McCann, M. F.; Ahmad, N.
Source: Contraception. 22(6):573–582, December 1980.

Published Abstract: Results are reported of a clinical trial of Neo Sampoon® vaginal contraceptive tablets, conducted by the International Fertility Research Program (IFRP) in collaboration with the Dacca Medical College Hospital, Bangladesh. Of the 150 women enrolled, 115 remained in the study at the end of 12 months. The 12-month cumulative gross life-table rates per 100 women were 6.5 for pregnancy and 24.8 for discontinuation due to other reasons. Discomfort associated with heat generated by the tablets' effervescence was the primary side effect of Neo Sampoon® use, and was one of the major causes of discontinuation. Regularity of use an acceptability of this foaming tablet appeared to be high compared to other barrier methods. Further research is needed on Neo Sampoon® and other vaginal contraceptives to develop and promote methods that can help meet the worldwide demand for fertility control.

II.B.ii–2
A User Acceptability Study of Vaginal Spermicides in Combination With Barrier Methods or an Intrauterine Device.
Author: Black, C.; Houghton, V. P.

Form: Journal Article.
Author: Black, C.; Houghton, V. P.
Source: Contraception. 28(2):103–110, 1983.

Abstract: Ninety–eight women were entered into an open study of Staycept® jelly (octoxynol, 1% w/w) and Staycept® pessaries (vaginal suppositories) (nonoxynol–9, 6% w/w) in combination with other vaginal methods of contraception. Medical problems during use of either pessary or jelly were few and were restricted to genital irritation or increased vaginal discharge. This seemed more common with the pessaries than with the jelly, but this could have been related to the types of women entered. There were no unplanned pregnancies.

II.B.ii–3
A Comparative Study of the Safety, Effectiveness and Acceptability of Two Foaming Vaginal Tablets (Nonoxynol–9 Versus Menfegol) in Thai Women.

Form: Journal Article.
Author: Chompootaweep, S.; Dusitsin, N.
Source: Contraception. 41(5):507–517, May 1990.

Published Abstract: Two foaming vaginal tablets containing nonoxynol–9 (OVT–n) or menfegol (OVT–m) were studied to evaluate safety, effectiveness, and acceptability. The study was conducted at the Chulalongkorn University, Institute of Health Research, Bangkok, Thailand. A total of 102 women were randomly assigned to one of the two types of tablets and scheduled for follow–up visits at 1, 3, 6, and 12 months. Although there were differences between the two groups in the gross cumulative 12–month life table rates and 12–month continuation rates, they were not statistically significant. The 12–month discontinuation rates for accidental pregnancy were 31.7 per 100 women for the OVT–n group and 25.3 per 100 women for the OVT–m group. Of the 22 pregnancies that occurred, 17 were the result of use failure. This study indicates that regular and proper use of OVT–n or OVT–m tablets provides a safe and comparable means of birth control. Although a few product–related or medical complaints (e.g., burning) were reported by both groups of tablet users, it seems that the foaming vaginal tablet is an acceptable method for fertility control in a suitable population who will use it regularly and properly.

II.B.ii–4
Frequent Use of Menfegol Spermicidal Vaginal Foaming Tablets Associated With a High Incidence of Genital Lesions.

Form: Journal Article.
Author: Goeman, J.; Ndoye, I.; Sakho, L. M.; Mboup, S.; Piot, P.; Karam, M.; Belsey, E.; Lange, J. M.; Laga, M.; Perriens, J. H.

Source: Journal of Infectious Diseases. 171(6):1611–14, June 1995.

Published Abstract: Menfegol is a spermicide with in vitro activity against human immunodeficiency virus (HIV). A randomized placebo-controlled safety study covered the use of menfegol foaming tablets for 14 days, at increasing frequencies of insertion, by 125 prostitutes in Dakar, Senegal. The frequencies of colposcopically diagnosed genital lesions were 5.0%, 11.8%, 27.8%, 49.7%, and 29.4% among menfegol recipients when tablets were used once every other day or 1, 2, 4, or 8 times a day, respectively ($P < .05$). Among placebo recipients, frequencies were 11.1% and 23.5% when tablets were used < 8 times daily and 8 times daily, respectively. There was no association between subjective genital symptoms and the incidence of colposcopically detected lesions. The high incidence of genital lesions when menfegol foaming tablets were used more than once daily suggests that their frequent use should not be recommended to prevent HIV transmission. In use at low frequency, the tablets' toxicity might be balanced by anti-HIV properties. Safety studies on vaginal microbicides should use objective methods, such as colposcopy, to assess the incidence of lesions.

II.B.ii–5
A Phase I Study of Curdlan Sulfate—An HIV Inhibitor. Tolerance, Pharmacokinetics and Effects on Coagulation and on CD4 Lymphocytes.

Form: Journal Article.
Author: Gordon, M.; Guralnik, M.; Kaneko, Y.; Mimura, T.; Baker, M.; Lang, W.
Source: Journal of Medicine. 25(3–4):163–180, 1994.

Published Abstract: Curdlan sulfate (CRDS) is a semisynthetic sulfated polysaccharide that is active against human immunodeficiency virus (HIV) in vitro and that inhibits attachment of the virus to T cells. After 2 weeks of exposure of virus and cells to CRDS, there is complete inhibition of virus replication. CRDS is also active against cytomegalovirus. The favorable toxicological profile of CRDS in animals suggested clinical trials. In this study, doses of 0.014, 0.14, 0.42, 1.42, 2.84, and 4.26 mg/kg (hereinafter referred to as 1, 10, 30, 100, 200, and 300 mg/body, respectively, for convenience) were administered to three HIV–positive patients at each dose level for 4 hours intravenously. Activated partial thromboplastin times (APTT) were measured hourly. Unexpectedly, single doses of CRDS produced marked, dose–related increases in CD4 lymphocytes in HIV–infected patients. There were no clinical side effects seen at any dose tested. All laboratory parameters were normal except for prolongation of APTT in the 200– and 300–mg dose groups. Two patients in the 300–mg dose group had a doubling of the APTT during the 4–hour infusion, which was the termination point of the trial according to the protocol. The half–life of CRDS was estimated to be 2–3 hours on the basis of the APTT data and the blood level assays (not shown). CRDS was well–tolerated in the study, with the APTT levels providing a convenient monitoring basis for dosing. Marked increases in CD4 levels were seen at higher doses, which, if confirmed and extended, may have therapeutic implications. CRDS is considered safe for multiple dosing with monitoring of APTT.

II.B.ii–6
Local Treatment of Colpitis With Betadine® Vaginal Suppository.

Form: Journal Article.
Author: Resch, B. A.; Szanto, F.
Source: Therapia Hungarica. 41(4):137–140, 1993.

Published Abstract: None.
Annotator's Abstract: The authors studied the effects of Betadine® vaginal suppository in the treatment of 60 women with colpitis. They compared the results of microbiologic examinations of vaginal discharge sampled 1 week before and 4 weeks after therapy was begun. The effectiveness, women's ability to tolerate the therapy, and subjective opinions of the treated women were analyzed. In response to Betadine® vaginal suppository treatment, the positivity of vaginal discharge for candida decreased from 16 cases to 3; for trichomonas, from 8 cases to 1; for aerobic bacteria, from 16 cases to 7; and for mixed infections, from 20 cases to 2. Subjective complaints such as burning and stinging sensations were rapidly moderated. In 52 of the 60 women, discharge ceased; in another 4, it decreased significantly. In 51 women, the burning sensation in the vagina ceased, and in 5 women, it decreased

significantly. Recurrence was not observed when a control examination was done 1 month after testing. The women tolerated the Betadine® vaginal suppository well and found it effective and easily applicable. At the beginning of treatment, burning sensation was aggravated in three women. These patients refused to participate further in the study and received systemic treatment. Because of its broad bactericidal, fungicidal, and protozoacidal action and the fact that women can tolerate it, Betadine® suppository was found to be useful for the local treatment of colpitis.

II.B.ii–7
[Real and False Risk of Local Contraception: Spermicides and the Diaphragm.] [French.]
Author: Zufferey, M. M.
[See abstract IV.A–35.]

II.B.ii–8
Nonoxynol-9 Lubricated Latex Condoms May Increase Release of Natural Rubber Latex Protein.

Form: Journal Article.
Author: Stratton, P.[1]; Hamann, C.[2]; Beezhold, D.[3] [1]NICHD, Bethesda, MD; [2]Smart Practice, Phoenix, AZ; [3]Guthrie Institute, Sayre, PA.
Source: Th.C.433, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: Recognition of genital tract irritation to nonoxynol-9 (N-9) with use of spermicides and N-9-lubricated condoms has raised questions about N-9's safety and role in preventing HIV transmission. Irritation may also be due to an increased elution of natural rubber latex (NRL) proteins by N-9. *Methods*: 5 brands of condoms using lubricants with and without N-9 were evaluated. Two nonlatex brands (Tactylon™) using lubricants with and without N-9 served as controls. NRL protein content was measured using Lowry and Latex ELISA for Antigenic Protein (LEAP) assays. Condoms and lubricants were tested in triplicate seven to ten different times. *Results*: NRL protein levels in condoms varied from brand to brand. Using the Lowry assay, a 5-fold increase in protein levels was detected for brands plus N-9 when compared to the brand minus N-9 from the same manufacturer. The LEAP assay confirmed a 4-fold increase in NRL protein levels for those with N-9 when compared to those without N-9. Lowry tests on Tactylon™(a nonprotein polymer) were positive in those with N-9 but negative in those without. The LEAP assay did not detect any NRL protein in Tactylon™. *Conclusions*: Protein tests demonstrated that N-9 lubricated latex condoms had significantly higher NRL protein levels. N-9 may cause increases in the value or false positive results on Lowry. N-9 may increase NRL protein extraction from latex which may increase the risk of developing latex hypersensitivity. Further study is warranted about the interaction between lubricants and latex condoms packaged together. From a public health view, this could alter condom manufacturing processes, could modify regulatory oversight for existing latex condoms, and underscores the need to develop new, non-latex condoms.

II.C.*i*.a. Clinical Studies of Effectiveness Against STD–Nonoxynol–9.

II.C.i.a–1
Confidential HIV Testing and Condom Promotion in Africa. Impact on HIV and Gonorrhea Rates.
Author: Allen, S.; Serufilira, A.; Bogaerts, J.; Van–de–Perre, P.; Nsengumuremyi, F.; Lindan, C.; Carael, M.; Wolf, W.; Coates, T.; Hulley, S.
[See abstract III.A–1.]

II.C.i.a–2
A Case–Control Study of Spermicides and Gonorrhea.

Form: Journal Article.
Author: Austin, H.; Louv, W. C.; Alexander, W. J.
Source: JAMA. 251(21):2822–24, June 1, 1984.

Published Abstract: A case–control study was done to evaluate the effectiveness of vaginal spermicides as a prophylaxis against gonorrhea. Subjects included 735 women with gonorrhea and 958 controls seen in a sexually transmitted disease clinic. The relative risk (RR) of gonorrhea for spermicide users compared with nonusers was 0.67 (90% confidence interval (CI) 0.44–1.0). After the exclusion of women who were using oral contraceptives or an intrauterine device or who had a tubal ligation, the RR was 0.47. The protective effect of spermicides was confined largely to women who had also used diaphragms or whose partners had used condoms. The RR of gonorrhea for spermicide and condom users relative to nonusers of spermicides, condoms, and diaphragms was 0.41 (90% confidence limits, 0.21 to 0.79), while for spermicide and diaphragm users, this RR was 0.45 (90% confidence limits, 0.15 to 1.3). These results suggest that a woman can appreciably decrease her risk of contracting gonorrhea if she uses spermicide in conjunction with either the diaphragm or the condom.

Commentary: Protective effect of spermicides alone was not demonstrated (RR= 0.8, 90% CI 0.52–1.0).

II.C.i.a–3
A Follow-Up Study of Methods of Contraception, Sexual Activity, and Rates of Trichomoniasis, Candidiasis, and Bacterial Vaginosis.

Form: Journal Article.
Author: Barbone, F.; Austin, H.; Louv, W. C.; Alexander, W. J.
Source: American Journal of Obstetrics & Gynecology. 163(2):510–514, August 1990.

Published Abstract: A randomized, clinical trial was conducted to evaluate the spermicidal agent nonoxynol–9 as prophylaxis for sexually transmitted diseases. Eight–hundred and eighteen women using birth control who attended a sexually transmitted disease clinic were evaluated monthly for trichomoniasis, candidiasis, and bacterial vaginosis for 6 months. Women using the active spermicide experienced a somewhat lower incidence rate of trichomoniasis (relative rate (RR) 0.83; 95% confidence interval (CI), 0.61–1.12) and bacterial vaginosis (RR 0.86; 95% CI, 0.69–1.12) as compared with placebo users. The rate of candidiasis was nearly identical for spermicide and placebo users (RR 1.02; 95% CI, 0.77–1.35). The number of sexual partners during the preceding month was related directly to the occurrence of trichomoniasis ($p = 0.047$) and bacterial vaginosis ($p = 0.009$) but not candidiasis ($p = 0.99$). Subjects using oral contraceptives experienced a statistically significant lower rate of trichomoniasis than did women using an intrauterine contraceptive device or who had had a tubal ligation (RR 0.56; 95% CI, 0.39–0.81).

II.C.i.a–4
Vaginal Spermicides and Gonorrhea.

Form: Journal Article.
Author: Jick, H.; Hannan, M. T.; Stergachis, A.; Heidrich, F.; Perera, D. R.; Rothman, K. J.
Source: JAMA. 248(13):1619–21, October 1, 1982.

Published Abstract: All positive cultures for *Neisseria gonorrhoeae* recorded from December 20, 1978, through December 31, 1980, for women born between 1940 and 1960 were identified among members of Group Health Cooperative of Puget Sound, Seattle. Rates of gonorrhea were calculated for recent oral

contraceptive users, recent vaginal spermicide users, and women with surgical sterilization. The risk ratio (RR) estimate, based on the included population, for spermicide users compared with all others was 0.23 (90% confidence interval (CI) 0.10–0.50). When women with positive cultures for *N. gonorrhoeae* were compared with women with negative cultures, the RR estimate comparing spermicide users with all others was 0.13 (90% CI 0.05–0.34). The results are consistent with a protective effect of vaginal spermicide against gonorrhea.

Commentary: This study suggests a reduction of approximately 75% in the rate of gonorrhea when comparing women who used spermicide and all other women; the estimates were not controlled for concurrent condom and diaphragm use.

II.C.i.a–5
The In Vivo Effects of Nonoxynol–9 Contraception on Vaginal Microbial Flora and Colonization With *Escherichia coli*.
Author: Jones, B. M.; Eley, A.
[See abstract I.F–3.]

II.C.i.a–6
Barrier Method Contraceptives and PID.

Form: Journal Article.
Author: Kelaghan, J.; Rubin, G. L.; Ory, H. W.; Layde, P. M.
Source: JAMA. 248(2):184–187, July 9, 1982.

Published Abstract: The protective effect of barrier method contraception against pelvic inflammatory disease (PID) was examined by analyzing data from the Women's Health Study, a large multicenter case–control study. The authors compared the contraceptive methods used by 645 women hospitalized for initial episodes of PID with the contraceptive methods used by 2,509 control subjects reporting no history of PID. The risk of hospitalization for PID in women currently using barrier methods relative to women using all other methods and to women using no method of contraception was 0.6 (95% confidence interval 0.5—0.9) for both comparisons. This protective effect was observed for both chemical and mechanical barrier methods, although it was not statistically significant for chemical methods. The prevention of PID and its sequelae is one of the most important noncontraceptive benefits of barrier methods of contraception.

II.C.i.a–7
Efficacy of Nonoxynol–9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes.

Form: Journal Article.
Author: Kreiss, J.; Ngugi, E.; Holmes, K.; Ndinya–Achola, J.; Waiyaki, P.; Roberts, P. L.; Ruminjo, I.; Sajabi R.; Kimata, J.; Fleming, T. R.; et al.
Source: JAMA. 268(4):477–482, July 22–29, 1992.

Published Abstract: Objective: The authors conducted a randomized, placebo–controlled trial to determine the efficacy of the nonoxynol–9 contraceptive sponge in preventing sexual acquisition of the human immunodeficiency virus (HIV). The study subjects were patients at a research clinic for prostitutes in Nairobi, Kenya. A total of 138 HIV–seronegative women were enrolled, of whom 74 were assigned to nonoxynol–9 sponge use and 64 to placebo use. These two groups did not differ significantly with respect to demographic characteristics, sexual practices, or prevalence of genital infections at enrollment, except for a lower number of sex partners per week and a higher initial prevalence of genital ulcers among women assigned to nonoxynol–9 sponge use. Among the 116 women who returned for follow–up, the mean duration of follow–up was 14 months for the nonoxynol–9 group and 17 months for the placebo group. The main outcome measure for the study was HIV seroconversion. Results: Use of the nonoxynol–9 sponge was associated with an increased frequency of genital ulcers (relative risk (RR) = 3.3; $P < 0.0001$) and vulvitis (RR = 3.3; $P < 0.0001$), and a reduced risk of gonococcal cervicitis (RR = 0.4; $P < 0.0001$). Twenty–seven (45%) of the 60 women in the nonoxynol–9 sponge group and 20 (36%) of 56 women in the placebo group developed HIV antibodies. The hazard ratio for the association between nonoxynol–9 sponge use and HIV seroconversion was 1.7 (95% confidence interval (CI) 0.9–3.0). Using multivariate analysis to control for the presence of genital ulcers at enrollment, the adjusted hazard ratio for the association between nonoxynol–9 sponge use and seroconversion was 1.6 (95% CI 0.8–2.8). The authors concluded that genital

ulcers and vulvitis occurred with increased frequency in nonoxynol–9 sponge users. The conclusion was that nonoxynol–9 sponge use was not effective in reducing the risk of HIV infection among highly exposed women.

II.C.i.a–8
Resolution of Resistant Vaginal Trichomoniasis Associated With the Use of Intravaginal Nonoxynol–9.

Form: Journal Article.
Author: Livengood III, C. H.; Lossick, J. G.
Source: Obstetrics and Gynecology. 78(5 pt 2):954–956, November 1991.

Published Abstract: An otherwise healthy, sexually inactive woman was determined by in vitro susceptibility testing to have vaginal infection by a strain of *Trichomonas vaginalis* with high–grade resistance to metronidazole. Prolonged oral and intravaginal therapy with high doses of metronidazole did not resolve the infection, but caused temporary peripheral neuropathy. Tinidazole was ineffective as well. Serendipitous use of topical intravaginal nonoxynol–9 for contraception appeared to resolve the infection. Possible causes of falsely "resistant" trichomoniasis—reinfection, noncompliance with therapy, and concomitant use of other drugs that degrade the efficacy of metronidazole—were reviewed. The literature suggests that mebendazole, furazolidone, and anisomycin may be effective for treatment of metronidazole–resistant trichomoniasis. This case and previously published laboratory data suggest that intravaginal nonoxynol–9 deserves further study as a treatment for resistant trichomoniasis, although trichomonal coinfection of the patient's urethra, Skene's glands, and sexual partner would not likely be resolved by such therapy.

II.C.i.a–9
A Clinical Trial of Nonoxynol–9 for Preventing Gonococcal and Chlamydia Infections.

Form: Journal Article.
Author: Louv, W. C.; Austin, H.; Alexander, W. J.; Stagno, S.; Cheeks, J.
Source: Journal of Infectious Diseases. 158(3):518–523, September 1988.

Published Abstract: A randomized, double–blind, placebo–controlled trial was conducted to evaluate the spermicidal agent nonoxynol–9 as a prophylaxis for cervical infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae.* Eight hundred and eighteen women were recruited from a sexually transmitted disease clinic. Only subjects between the ages of 19 and 29 years using reliable birth control method (oral contraceptives, intrauterine devices, or sterilization) were eligible. Subjects were randomly assigned to use either a commercially available spermicidal agent containing nonoxynol–9 or a placebo preparation. Subjects were followed up for 6 months; specimens were collected monthly for culture of the two pathogens. Women assigned to the nonoxynol–9 group were less likely to become infected with *N. gonorrhoeae* (relative rate, 0.75; 90% confidence limits, 0.58 and 0.96) and *C. trachomatis* (relative rate, 0.79; 90% confidence limits, 0.64 and 0.97). Among women who used the assigned gel for the majority of coital episodes, a stronger protective effect was observed.

II.C.i.a–10
Use of Nonoxynol–9 and Reduction in Rate of Gonococcal and Chlamydial Cervical Infections.

Form: Journal Article.
Author: Niruthisard, S.; Roddy, R. E.; Chutivongse, S.
Source: Lancet. 339(8806):1371–75, June 6, 1992.

Published Abstract: The spermicide nonoxynol–9 has been used as a contraceptive for more than 30 years, but the use of a vaginal spermicide and condoms for the prevention of sexually transmitted infections has not been examined in randomized studies. The authors report a single–blind, randomized field trial to assess the effect of nonoxynol–9 film on the rate of gonococcal and chlamydial cervical infection in women at high risk for these diseases. A total of 343 women were randomly assigned to use either condoms and nonoxynol–9 (186 women) or condoms and a placebo (157). Compliance with condom use was much the same in the two groups. Overall, nonoxynol–9 reduced the rate of cervical infection by 25% (rate ratio (RR), 0.75, 95%

confidence interval (CI) 0.5–1.1); in women who used nonoxynol–9 for more than 75% of their coital acts, the infection rate was reduced by 40% (RR, 0.60; 95% CI 0.3–1.0). The rate of yeast vulvovaginitis or genital ulcers in the nonoxynol–9 users was not higher than that in the placebo users, but the rate of symptomatic irritation was increased by 70% (RR 95% CI 1.1–2.6) among nonoxynol–9 users. Condom use was more protective against cervical infection than nonoxynol–9 use. The rate of infection was 50% (RR, 0.5; 95% Cl 0.3–0.7) lower with 75% condom compliance than with 0–50% condom compliance. The use of a vaginal nonoxynol–9 spermicide with condoms, whenever possible, seems to be a better strategy than the use of condoms only for prevention of gonococcal and chlamydial cervical infection.

II.C.i.a–11
"PROTECTAID"®: A New Vaginal Sponge With Contraceptive and Antiviral Properties.
Author: Psychovos, A.; Creatsas, G.; Hassan, E.; Georgoulias, V.; Gravanis A.
[See abstract II.C.i.b–9.]

II.C.i.a–12
Barrier Contraceptives and Sexually Transmitted Disease in Women: A Comparison of Female–Dependent Methods and Condoms.

Form: Journal Article.
Author: Rosenberg, M. J.; Davidson, A. J.; Chen, J. H.; Judson, F. N.; Douglas, J. M.
Source: American Journal of Public Health. 82:669–674, 1992.

Published Abstract: Introduction: Most efforts at sexually transmitted disease (STD) protection center on condom use, but little is known about how condoms compare with other barrier methods, particularly those controlled by women. Methods: To evaluate the effect of different barrier contraceptives on the prevalence of STDs and other vaginal infections, the authors retrospectively studied 5,681 visits by women to an urban STD clinic. Results: As compared with women not using contraceptives or with tubal ligations, women using the contraceptive sponge or diaphragm had at least 65% lower rates of infection with *N. gonorrheae* and *Trichomonas vaginalis*, while condom users had 34% and 30% lower rates, respectively. For *Chlamydia trachomatis*, the reduction was 13% among sponge users, 72% among diaphragm users, and 3% among condom users, although these differences were not significant. When compared with women using condoms, women using female–dependent methods (sponge or diaphragm) had significantly lower rates of both gonorrhea and trichomoniasis. Vaginal candidiasis was more common among women using diaphragms but not other barrier methods, while rates of bacterial vaginosis were similar among all groups. Conclusion: Women using the contraceptive sponge or diaphragm experienced protection from STDs to a greater extent than those relying on condoms. Female–dependent barrier contraceptives should receive more attention in STD risk reduction programs.

II.C.i.a–13
The Contraceptive Sponge's Protection Against *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Form: Journal Article.
Author: Rosenberg, M. J.; Feldblum, P. J.; Rojanapithayakorn, W.; Sawasdivorn, W.
Source: Sexually Transmitted Diseases. 14(3):147–152, July–September 1987.

Published Abstract: To investigate the effect of the contraceptive sponge on the incidence of sexually transmitted diseases, we conducted a clinical trial among a high-risk population of women in Bangkok, Thailand. Two hundred fifty-five women were randomly assigned either to use the sponge or not and were evaluated weekly for gonorrhea and chlamydial infection. After adjustment by logistic regression for potentially confounding factors, women using the sponge were less likely to have contracted chlamydial infection (odds ratio (OR), 0.6; 90% confidence interval (CI, 0.4–1.0) and gonorrhea (OR, 0.9; CI, 0.6–1.3) as compared with women not using the sponge. These estimates probably underestimate the degree of protection because some exposure was misclassified in this pilot phase of the study. These results are consistent with other studies indicating that spermicides protect against gonorrhea and also demonstrating protection against an organism of even greater public health concern, *Chlamydia trachomatis*.

II.C.i.a–14
Effect of the Contraceptive Sponge on Chlamydial Infection, Gonorrhea, and Candidiasis: A Comparative Clinical Trial.

Form: Journal Article.
Author: Rosenberg, M. J.; Rojanapithayakorn, W.; Feldblum, P. J.; Higgins, J. E.
Source: JAMA. 257(17):2308–12, May 1, 1987.

Published Abstract: To investigate the effect of the nonoxynol–9-impregnated contraceptive sponge on the incidence of chlamydial infection, gonorrhea, and candidiasis, we conducted a randomized comparative study among high-risk women in Bangkok, Thailand. The first (parallel) portion of the study covered 434 woman-weeks among sponge users and 494 woman-weeks among nonusers. As compared with women not using the sponge, sponge users were found to be less likely to become infected with chlamydia (relative rate, 0.67; 95% confidence interval (CI), 0.42 to 1.07) and gonorrhea (relative rate, 0.31; CI, 0.16 to 0.60)) but more likely to become infected with Candida (relative rate, 2.76; CI, 0.96 to 7.98). Women who continued in the study were crossed over to the alternate group, with former nonusers starting to employ the sponge and vice versa. The results of this second phase were similar to those of the larger parallel study. Overall, these results suggest that women using the sponge are protected against the two most common sexually transmitted pathogens, which are also those with the most serious health consequences. However, women using the sponge should be advised they may have an increased likelihood of a vaginal infection with Candida.

II.C.i.a–15
Sexual Practices in the Transmission of Hepatitis B Virus and Prevalence of Hepatitis Delta Virus Infection in Female Prostitutes in the United States.

Form: Journal Article.
Author: Rosenblum, L.; Darrow, W.; Witte, J.; Cohen, J.; French, J.; Gill, P. S.; Potterat, J.; Sikes, K.; Reich, R.; Hadler, S.
Source: JAMA. 267(18):2477–81, May 13, 1992.

Published Abstract: Objective: The authors conducted a serosurvey to evaluate the heterosexual transmission of hepatitis B virus (HBV) and the prevalence of hepatitis delta virus (HDV) infection in female sex workers. Methods: A total of 1,368 female prostitutes 18 years of age or older were contacted through sexually transmitted disease (STD) clinics, drug treatment programs, detention centers, and other outreach efforts in eight areas in the United States. The outcome measures in the study were seropositivity for HBV and HDV infection. Results: The overall prevalence of past or present HBV infection was 56%: 74% in women who were injecting drug users (IDUs), 38% in women reporting no history of injecting drug use (non–IDUs), 51% in whites, 55% in blacks, and 67% in Hispanics. Of 21 HBV–carrier IDUs, 21% had HDV infection; of 18 HBV–carrier non–IDUs, 6% had HDV infection. In non–IDUs (49%), risk factors for HBV infection were a history of having penile–anal intercourse (odds ratio (OR), 3.1; 95% confidence interval (CI) 1.3–7.3) and seropositivity for syphilis and human immunodeficiency virus (HIV) infection. In IDUs, factors associated with an increased risk of infection, in addition to behaviors related to injecting drug use, were the number of lifetime sexual partners, having sexual partners from groups at high risk for HBV infection, and seropositivity for syphilis and HIV; spermicide and/or diaphragm use was associated with a markedly decreased risk of HBV infection among blacks (OR, 0.1; 95% CI 0.03–0.4) and Hispanics (OR, 0.2; 95% CI 0.06–0.9). This is the first study to suggest that having anal intercourse and failing to use vaginal contraceptives may facilitate transmission of HBV to women. This reinforces guidelines that recommend hepatitis B vaccination for prostitutes and persons with a history of STDs or multiple sexual partners.

II.C.i.a–16
The Use of Nonoxynol–9 for Protection Against Cervical Gonorrhea.

Form: Journal Article.
Author: Weir, S. S.; Feldblum, P. J.; Zekeng, L.; Roddy, R. E.
Source: American Journal of Public Health. 84(6):910–914, June 1994.

Published Abstract: Objectives: Although condoms are the best defense against sexually transmitted disease, little is known about the effectiveness of female–controlled methods containing nonoxynol–9 as backup protection when condoms are not being used. Methods: To assess the extent to which nonoxynol–9 protects women against gonorrhea, a cohort of 303 female sex workers (prostitutes) in Yaounde, Cameroon, were asked to use condoms and suppositories containing 100 mg of nonoxynol–9 at every sexual encounter and to record daily sexual activity and use of condoms and suppositories on coital logs that were reviewed monthly. The other ingredients in the suppository were polyethylene glycol, benzalkonium chloride, citric acid, D&C red no. 21, D&C red no. 3, methylparaben, and water. Stratified analysis and proportional hazards regression were used to estimate rate ratios. Results: Forty–one women who were enrolled in the study were excluded from the current analysis. The estimated incidence of gonorrhea was 6.2 infections per 100 person–months of observation. Incidence rate ratios estimated from proportional hazards regression models controlling for condom use showed that using nonoxynol–9 during acts not protected by condoms reduced the risk of infection. Although the protective effect of condoms against sexually transmitted disease is greater than that afforded by nonoxynol–9, using nonoxynol–9 when condoms are not used is a far better strategy in gonorrhea prevention than using no method at all.

Commentary: This study population is the same as that reported in Zekeng et al. (AIDS, 1993). The authors noted that the lack of randomization to either condom or nonoxynol–9 use and the reliability of coital logs had an impact on the study results.

II.C.i.a–17
Nonoxynol–9 Use, Genital Ulcers, and HIV Infection in a Cohort of Sex Workers.
Author: Weir, S. S.; Roddy, R. E.; Zekeng, L.; Feldblum, P. J.
[See abstract II.B.i–26.]

II.C.*i.*b. Clinical Studies of Effectiveness Against STD–Other Spermicides.

II.C.i.b–1
The Effect of Bacteriostatic Lubricant on Group B Streptococcal Cultures of the Female Genital Tract.

Form: Journal Article.
Author: Brady, K.; Sizemore, K. L.; Duff, P.; Aamodt, L. W.
Source: Obstetrics & Gynecology. 74(6):848–850, December 1989.

Published Abstract: The purpose of this prospective investigation was to determine the effect of bacteriostatic lubricant on group B streptococcal cultures obtained from the lower genital tract of pregnant women. Fifty pregnant women with intact membranes who recently had genital tract cultures for group B streptococci were evaluated. The study group consisted of 25 women who had positive cultures, and the control group comprised 25 women who had negative cultures. All patients underwent examination with a sterile nonlubricated speculum within 7 days of the previously obtained cultures. Secretions from the endocervix and from the posterior vaginal wall near the introitus were collected with a sterile cotton-tipped applicator and inoculated directly onto a selective blood agar culture plate. The sterile speculum was removed and a digital examination performed using bacteriostatic lubricant. A second sterile speculum was then inserted into the vagina and another group B streptococcal culture was obtained. There was 100% correlation between the cultures obtained before and after the vaginal examination. We conclude that use of bacteriostatic lubricant does not alter the recovery of group B streptococci from the genital tract of pregnant women with intact membranes.

II.C.i.b–2
Prevention of Excess Neonatal Morbidity Associated With Group B Streptococci by Vaginal Chlorhexidine Disinfection During Labor.

Form: Journal Article.
Author: Burman, L. G.; Christensen, P.; Christensen, K.; Fryklund, B.; Helgesson, A. M.; Svenningsen, N. W.; Tullus, K. Swedish Chlorhexidine Study Group.
Source: Lancet. 340(881):65–69, July 11, 1992.

Published Abstract: *Streptococcus agalactiae* transmitted to infants from the vagina during birth is an important cause of invasive neonatal infection. The authors have done a prospective, randomized, double–blind, placebo–controlled, multicenter study of chlorhexidine prophylaxis to prevent neonatal disease due to vaginal transmission of *S. agalactiae*. On arrival in the delivery room, swabs were taken for culture from the vaginas of 4,483 women who were expecting a full–term single birth. Vaginal flushing was then done with either 60 ml chlorhexidine diacetate (2g/l) (2,238 women) or saline placebo (2,245 women); this procedure was repeated every 6 hours until delivery. The rate of admission of babies to special–care neonatal units within 48 hours of delivery was the primary end point. For babies born to placebo–treated women, maternal carriage of *S. agalactiae* is associated with a significant increase in the rate of admission compared with non–colonized mothers (5.4 vs 2.4%; RR 2.31, 95% CI 1.39–3.86; p = 0.002). Chlorhexidine reduced the admission rate for infants born of carrier mothers to 2.8% (RR 1.95, 95% CI 0.94–4.03) and for infants born to all mothers to 2.0% (RR 1.48, 95% CI 1.01–2.16; p = 0.04). Maternal *S. agalactiae* colonization is associated with excess early neonatal morbidity, apparently related to aspiration of the organism, that can be reduced with chlorhexidine disinfection of the vagina during labor.

II.C.i.b–3
Vaginal Chlorhexidine Disinfection During Labor.

Form: Journal Article, Letter.
Author: Feldman, R.; Van Oppen, C.; Noorduyn, A.
Source: Lancet. 340(8822):791–792, September 26, 1992.

Published Abstract: None.
Annotators' Abstract: The authors critique the article by Dr. Burman and colleagues (Lancet, July 11, 1992, p. 65) on vaginal chlorhexidine disinfection during labor. They claim that the Burman data do not show an association between the morbidity prevented by

chlorhexidine and group B streptococci.

II.C.i.b–4
[Benzalkonium in Local Contraception and Sexually Transmitted Diseases.] [Italian.]

Form: Journal Article.
Author: Frateschi, M.; Zandonini, G. F.; Mazzoleni, G. C.
Source: Annali di Ostetricia, Ginecologia, Medicina Perinatale. 111(4):265–269, July–August 1990.

Published Abstract: None.
Annotators' Abstract: The authors studied the use of a benzalkonium–treated sponge as a local contraceptive in 96 women in ambulatory care followed from 1983 through 1986. This substance has not only shown itself to be a good contraceptive, but may even prove to be useful against sexually transmitted diseases.

II.C.i.b–5
A Clinical Trial of a Vaginal Preparation Regimen for the Prophylaxis of Gonorrhea.

Form: Journal Article.
Author: Limsuwan, A.; Vachrotai, S.; Panupornprapong, Y.; Buasuang, S.; Panichayanusonthi, O.; Achananuparp, S.; Nanna, P.; Unhanantha, M.
Source: Journal of the Medical Association of Thailand. 61(8):435–440, August 1978.

Published Abstract: None.
Annotators' Abstract: This study was a nonrandomized clinical trial of commercial sex workers in Thailand who used vaginal povidone iodine rinse. The relative rate (RR) for gonorrhea was 0.25 (CI 0.15–0.42).

II.C.i.b–6
Vaginal Chlorhexidine Disinfection During Labour.

Form: Journal Article, Letter.
Author: Lindemann, R.; Henrichsen, T.; Svenningesen, L.; Hjelle, K.
Source: Lancet. 340(8822):792, September 26, 1992.

Published Abstract: None.
Annotators' Abstract: In a study of 3,236 women, these authors found similar levels of neonatal septicemia in infants born to women treated with a vaginal lavage of chlorhexidine diacetate versus an application of chlorhexidine gluconate obstetrical cream.

II.C.i.b–7
Prevention of Sexual Transmission of AIDS/STD by a Spermicide Containing Benzalkonium Chloride.

Form: Journal Article.
Author: Mendez, F.; Castro, A.
Source: Archives of AIDS Research. 4(1–2):115–135, 1990.

Published Abstract: The authors studied the effectiveness of a spermicide containing benzalkonium chloride (BK) in preventing infection with human immunodeficiency virus (HIV) and sexually transmitted diseases (STDs). Spermicides widely used in contraception, such as nonoxynol–9 and BK, have a preventive effect on the sexual transmission of HIV and STDs. In vitro inactivation of HIV by BK was obtained within 10 minutes of contact at 0.025%–0.08% concentration. BK inactivated sperm at concentrations of 0.03 to 0.08%. The most active of all spermicides tested, nonoxynol–9, inactivated HIV at 0.05% after 30 minutes. A vaginal pharmaceutical form of BK at 1.2% inactivates at 0.012% (Pasteur Institute, 1987). HIV survived inside latex condoms, but no free HIV–1 survived exposure to the interior of condoms lubricated with BK at 0.83% (Wainberg, 1988). The authors studied 903 high–risk women using a pharmaceutical preparation of BK during a 3–6 month period in order to quantify any preventive effect of BK against STDs (P = 0.001). The control group comprised high–risk women not treated with the BK spermicide. Clinical, gynecological, microbiological, and serological tests were performed every 2 months. A 41.3% reduction (P ~ 0.001) in the number of STD cases was observed; however, a consistent use was unrealistic and some positive diagnoses could be related to individual sexual practices (oral, anal) not covered by an intravaginal locally active product. The authors conclude that BK is an effective inactivator of HIV in vitro and provides protection against STDs.

II.C.i.b–8
Quantitative and Qualitative Effects of Povidone–Iodine Liquid and Gel on the

Aerobic and Anaerobic Flora of the Female Genital Tract.

Form: Journal Article.
Author: Monif, G. R.; Thompson, J. L.; Stephens, H. D.; Baer, H.
Source: American Journal of Obstetrics and Gynecology. 137(4):432–438, June 15, 1980.

Published Abstract: Povidone–iodine solution (Betadine Solution®) produces a dramatic reduction in the numbers of total aerobes and anaerobes recoverable from the posterior vaginal pool in the first 10 minutes following administration. Within 30 to 120 minutes, near baseline counts for both aerobic and anaerobic bacteria are reestablished. When the vehicle for the povidone–iodine is changed to polyethylene glycol (Betadine Vaginal Gel®), an effective antibacterial effect can be documented over a 3–hour period.

II.C.i.b–9
"PROTECTAID"®: A New Vaginal Sponge With Contraceptive and Antiviral Properties.

Form: Abstract.
Author: Psychovos, A.; Creatsas, G.; Hassan, E.; Georgoulias, V.; Gravanis A.
Source: International Conference on AIDS. 9(2):740 (abstract no. PO-C22-3140), June 6–11, 1993.

Authors' Abstract: Sodium cholate exhibits a strong spermicidal and anti-HIV-1 activity. The same effects are observed for F-5 Gel, the active mixture of a new contraceptive sponge, PROTECTAID®, which contains sodium cholate in association with low concentrations (0.5%) of nonoxynol-9 and benzalkonium chloride. Both sodium cholate and F-5 Gel exert a dose–dependant in vitro inhibitory effect (1) on the activity of HIV-1–associated reverse transcriptase in an acellular system, and (2) on the potential of HIV to efficiently infect human lymphocytes. During 12 months of use, the contraceptive efficacy of the PROTECTAID® sponge was 100% in 20 young women who chose this method for both contraceptive and anti-STDs purposes. No side effects were recorded throughout this period. Cervical cultures at 6 month intervals showed the presence of *Mycoplasma sp*. and *Candida albicans* in 1–2 cases. The PROTECTAID® sponge may offer a new and modern protective method.

II.C.i.b–10
Vaginal Contraception With Gossypol: A Clinical Study.

Form: Journal Article.
Author: Ratsula K.; Haukkamaa, M.; Wichmann, K.; Luukkainen, T.
Source: Contraception. 27(6):571–576, June 1983.

Published Abstract: A clinical study concerning the vaginal contraceptive efficacy of gossypol acetic acid was performed. Fifteen women who had undergone tubal sterilization volunteered for the study. The effect of vaginal gossypol-containing gel on spermatozoa was determined by postcoital tests performed in subjects without and after using gossypol gel. After gossypol application, the number of spermatozoa found in cervical mucus was greatly decreased; in 11 of the 15 women, all spermatozoa seen were immobilized. In four cases, a few poorly motile spermatozoa were seen but they showed no forward progression. We have previously reported that gossypol has an inhibitory effect on herpes simplex virus type 2 in vitro. This anti-viral property of gossypol makes it particularly attractive as a topical barrier contraceptive. The present study shows that gossypol is also promising as a vaginal contraceptive agent in human in vivo experiments.

II.C.i.b–11
Barrier Contraceptives and Sexually Transmitted Disease in Women: A Comparison of Female–Dependent Methods and Condoms.
Author: Rosenberg, M. J.; Davidson, A. J.; Chen, J. H.; Judson, F. N.; Douglas, J. M.
[See abstract II.C.i.a–12.]

II.C.*ii.*a. Clinical Studies of Effectiveness Against HIV–Nonoxynol–9.

II.C.ii.a–1
Confidential HIV Testing and Condom Promotion in Africa. Impact on HIV and Gonorrhea Rates.
Author: Allen, S.; Serufilira, A.; Bogaerts, J.; Van–de–Perre, P.; Nsengumuremyi, F.; Lindan, C.; Carael, M.; Wolf, W.; Coates, T.; Hulley, S.
[See abstract III.A–1.]

II.C.ii.a–2
Comment: The Use of Spermicide Containing Nonoxynol–9 in the Prevention of HIV Infection.

Form: Journal Article.
Author: Bird, K. D.
Source: AIDS. 5(7):791–796, July 1991.

Published Abstract: None.
Annotators' Abstract: This paper reviews the literature on the safety and efficacy of spermicides containing nonoxynol–9 used in contraception and in the prevention of human immunodeficiency virus (HIV) infection and sexually transmitted diseases (STDs). The author concludes that users need to be advised of the contraindications to the continued use of nonoxynol–9 and the use of spermicides for anal intercourse, a practice that has not been studied and cannot be recommended. The author calls for a distinction between the safety of nonoxynol–9 for contraceptive purposes and the safety of nonoxynol–9 in HIV prevention.

II.C.ii.a–3
Condom and Nonoxynol–9 Use and HIV Incidence in Serodiscordant Couples in Zambia.

Form: Abstract.
Author: Feldblum, P.; Hira, S.; Kamanga, J.; Mukelabai, G.; Weir, S.; Thomas, J. C.
Source: Abstract # 062 from Eleventh meeting of the International Society for STD Research, August 27–30, 1995, New Orleans, LA.

Published Abstract: None.
Annotators' Abstract: Preliminary report from a prospective study of 110 discordant couples; all couples were given condoms and their choice of 3 nonoxynol–9 (N–9)–containing products and advised to use both methods during each act of intercourse.During 17.6 months (mean) of follow–up, 14 HIV seroconversions occurred. Most couples used both methods; protection was correlated with consistent use of condoms but was not correlated with N–9.

II.C.ii.a–4
The Protective Effect of Nonoxynol–9 Against HIV Infection.

Form: Journal Article, Letter.
Author: Feldblum, P. J.; Weir, S. S.
Source: American Journal of Public Health. 84(6):1032–34, June 1994.

Published Abstract: None.
Annotators' Abstract: The authors reanalyzed data from a study of nonoxynol–9 among female sex workers (AIDS 7:725–731, 1993). The reanalysis suggests that when condoms are not used, the consistent use of a nonoxynol–9 spermicide can prevent HIV infection.

II.C.ii.a–5
Efficacy of the Simultaneous Use of Condoms and Spermicides.

Form: Journal Article.
Author: Kestelman, P.; Trussell, J.
Source: Family Planning Perspectives. 23(5):226–227, 232, September–October 1991.

Published Abstract: None.
Annotators' Abstract: The authors argue that the efficacy of two methods of contraception used together is higher than the product of the two probabilities of failure of each method. Their model predicts that perfect use—correct use at every act of intercourse—of condoms and spermicides may be as effective as steroidal implants for contraception; condoms also provide a high level of protection against sexually transmitted diseases.

II.C.ii.a–6
Efficacy of Nonoxynol–9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes.

Author: Kreiss, J.; Ngugi, E.; Holmes, K.; Ndinya–Achola, J.; Waiyaki, P.; Roberts, P. L.; Ruminjo, I.; Sajabi R.; Kimata, J.; Fleming, T. R.; et al.
[See abstract II.C.i.a–7.]

II.C.ii.a–7
The Effect of Contraceptives Containing Nonoxynol–9 on the Genital Transmission of Simian Immunodeficiency Virus in Rhesus Macaques.

Form: Journal Article.
Author: Miller, C. J.; Alexander, N. J.; Gettie, A.; Hendrickx, A. G.; Marx, P. A.
Source: Fertility and Sterility. 57(5):1126–28, May 1992.

Published Abstract: The ability of two nonoxynol–9 spermicide preparations to prevent the genital transmission of simian immunodeficiency virus (SIV) in rhesus macaques was compared. Administration of 1 ml of contraceptive foam (12.5% vol/vol) before the intravaginal inoculation of cell–free SIV prevented the genital transmission of SIV to three of six animals. The authors conclude that both contraceptive foams and gels containing nonoxynol–9 provided partial protection against the genital transmission of SIV.

II.C.ii.a–8
Nonoxynol–9 Use, Genital Ulcers, and HIV Infection in a Cohort of Sex Workers.
Author: Weir, S. S.; Roddy, R. E.; Zekeng, L.; Feldblum, P. J.
[See abstract II.B.i–26.]

II.C.ii.a–9
Barrier Contraceptive Use and HIV Infection Among High–Risk Women in Cameroon.

Form: Journal Article.
Author: Zekeng, L.; Feldblum, P. J.; Oliver, R. M.; Kaptue, L.
Source: AIDS. 7(5):725–731, May 1993.

Published Abstract: Objectives: The authors measured the association between spermicide use and human immunodeficiency virus (HIV) infection, adjusting for condom use, and the association between condom use and HIV infection, adjusting for spermicide use. Design: A prospective study of women using nonoxynol–9 spermicides and latex condoms, with up to 12 monthly clinic visits for interviews, examinations and tests, and re–supply was conducted. Methods: A total of 273 HIV–negative women with multiple sexual partners were enrolled, given latex condoms and nonoxynol–9 vaginal spermicidal suppositories, and advised to use both every time they had sexual intercourse. The participants recorded data on sexual activity in pictorial coital logs. New HIV infections were detected and confirmed by quarterly enzyme–linked immunosorbent assay (ELISA) and Western blots, respectively. Results: Nineteen HIV infections occurred during a mean followup of 8.1 months (an incidence rate of 10.4 infections per 100 women–years). The adjusted HIV rate ratio was 0.1 (95% confidence interval (CI) 0.1–0.6) for more consistent compared with less consistent spermicide users, and 1.1 (95% CI 0.4–2.9) for more consistent compared with less consistent condom users. Among the subgroup of experienced condom users, the HIV rate ratio for more versus less consistent condom use was 0.3. This is the first epidemiological evidence that nonoxynol–9 spermicides can reduce the incidence of HIV infection. A more definitive randomized clinical trial is urgently needed.

Commentary: The absence of a protective effect from using condoms to prevent the transmission of HIV may be related to how condom use was classified in this study. The implications of this categorization for spermicide analysis are unclear.

II.C.*ii.*b. Clinical Studies of Effectiveness Against HIV–Other Spermicides.

II.C.*iii.*a. Clinical Studies of Effectiveness Against Other Infections–Nonoxynol–9.

II.C.iii.a–1
Comparison of the Influence of Spermicidal and Nonspermicidal Contraception on Bacterial Vaginosis, Candidal Infection and Inflammation of the Vagina—A Preliminary Study.

Form: Journal Article.
Author: Jones, B. M.; Eley, A.; Hicks, D. A.; Patel, R.; Wordsworth, J. M.
Source: International Journal of STD and AIDS. 5(5):362–364, September–October 1994.

Published Abstract: This preliminary study compared the signs, symptoms, and prevalence of bacterial vaginosis (BV) and candidal infections in women using spermicides with those using other forms of contraception. The objective of the study was to establish whether nonoxynol–9 had any therapeutic value against BV or gave rise to vaginal candidiasis and inflammation. Results showed that the prevalence of BV in women not using spermicide was 35/113 (31%), but was significantly less in spermicide users (10/66 (15%), $P < 0.05$). Nonoxynol–9 use was not associated with increased isolation of *Candida albicans*, which was found in 16/113 (14%) of the women not using spermicide and in 8/66 (12%) of those using spermicides ($P > 0.1$). Vaginal inflammation and discharge were significantly less in spermicide users (19/66 (29%)) than in the group not using spermicide (50/113 (44%), $P < 0.05$). In conclusion, nonoxynol–9 use was associated with a significantly reduced prevalence of BV, but not with increased candidiasis or vaginal inflammation.

II.C.iii.a–2
Hydrogen Peroxide Production by *Lactobacillus* Species: Correlation With Susceptibility to the Spermicidal Compound Nonoxynol–9.
Author: McGroarty, J. A.; Tomeczek, L.; Pond, D. G.; Reid, G.; Bruce, A. W.
[See abstract I.F–7.]

II.C.*iii.*b. Clinical Studies of Effectiveness Against Other Infections–Other Spermicides.

II.C.iii.b–1
Topical Treatment for Bacterial Vaginosis.

Form: Journal Article.
Author: Anonymous.
Source: Medical Letter on Drugs and Therapeutics. 34(884):109, November 27, 1992.

Published Abstract: None.
Annotators' Abstract: This article summarizes the positive and adverse effects of two topical treatments for bacterial vaginosis: a 0.75% vaginal gel formulation of metronidazole and a 2% vaginal cream formulation of clindamycin phosphate. The author states that topical metronidazole and clindamycin for the treatment of bacterial vaginosis are as effective as oral metronidazole and better tolerated.

II.C.iii.b–2
Antimicrobial Effect of Chlorhexidine and Povidone–Iodine on Vaginal Bacteria.

Form: Journal Article.
Author: Vorherr, H.; Vorherr, U. F.; Mehta, P.; Ulrich, J. A.; Messer, R. H.
Source: Journal of Infection. 8(3):195–199, May 1984.

Published Abstract: The antimicrobial potency of 4% chlorhexidine gluconate was compared with that of 10% povidone–iodine (1% free iodine) on the vaginal bacteria of 150 premenopausal, nonpregnant women. Blood samples were taken from 30 of the women before and at either 15, 30, or 60 minutes after vaginal cleansing with chlorhexidine for chlorhexidine analysis. Five minutes after applying either chlorhexidine or povidone–iodine, almost 99% of the bacteria present on the lateral wall of the vagina were killed. Chlorhexidine was significantly more effective than povidone–iodine. Serosanguineous, mucoid, or white–yellowish vaginal discharge did not alter the effectiveness of either antimicrobial agent. In contrast to povidone–iodine, vaginally applied chlorhexidine was not absorbed in measurable amounts into the bloodstream (sensitivity of detection method: 0 x 1 mg/L). Chlorhexidine may therefore prove of value for treating vaginitis, especially during pregnancy, and also for combating microbes such as Group B streptococci, which are potentially harmful to the newly born child.

II.D.*i.* Clinical Studies of Administration, Dosage, Delivery–Nonoxynol–9.

II.D.i–1
Adverse Effects of Nonoxynol–9.
Author: Berer, M.
[See abstract II.B.i–3.]

II.D.i–2
Comment: The Use of Spermicide Containing Nonoxynol–9 in the Prevention of HIV Infection.
Author: Bird, K. D.
[See abstract II.C.ii.a–2.]

II.D.i–3
Preliminary Results, Serum Chemistry Values Before and After the Intravaginal Administration of 5% Nonoxynol-9 Cream.

Form: Journal Article.
Author: Malyk, B.
Source: Fertility & Sterility. 35(6):647–652, June 1981.

Published Abstract: Thirty-two healthy premenopausal women between the ages of 18 and 39 were randomly assigned to three study groups as follows: Group I received daily intravaginal administration of 2.5g of 5% nonoxynol-9 vaginal cream (Conceptrol (Ortho Pharmaceutical Corporation, Raritan, NJ) cream) for 14 days; Group II received daily intravaginal administration of 2.5g of the cream base alone; and Group III received no treatment. The numbers of subjects completing the study were 12, 11, and 7 (Groups I, II and III, respectively). Fasting blood samples were obtained from each subject prior to treatment and on days 8 and 15 after treatment. Blood samples were analyzed for 20 constituents, including proteins, lipids, triglycerides, and serum enzymes. There were no differences in any of the measured parameters between the pre- and post-treatment periods in any of the groups. On the basis of these findings it may be concluded that there are no apparent systemic effects following daily intravaginal administration of a 125-mg dose of nonoxynol-9 in a cream base for 2 weeks.

II.D.i–4
The Effects of Frequent Nonoxynol–9 Use on the Vaginal and Cervical Mucosa.
Author: Niruthisard, S.; Roddy, R. E.; Chutivongse, S.
[See abstract II.B.i–17.]

II.D.i–5
Assessment of a New Modified Soft Jelly Capsule Containing Nonoxynol as Spermicide Contraceptive.

Form: Journal Article.
Author: Recio, R.; Bassol, S.
Source: Advances in Contraception. 8(1):51–55, March 1992.

Published Abstract: The mean rupture time after vaginal insertion of a new, modified soft jelly capsule containing nonoxynol–9 (DF–486) was investigated in 40 women. The subjects were randomly allocated to eight study groups. The capsules remained in the vagina from 2 to 13 minutes. Vaginal infection, vaginal dryness, and multiparity were recorded. Capsule rupture was not observed at 2 minutes; 20% of capsules that remained in the vagina 3 minutes suffered rupture, as did 80% of capsules that remained 4, 5, and 7 minutes, and 100% of those remaining 9 minutes or more. The mean rupture time of the studied capsules was 8.2 minutes (95% confidence interval 6.2–8.8). At 2–7 minutes, vaginal infection, dryness, and tone diminution probably accounted for lack of rupture; after 7 minutes, these factors did not influence capsule rupture.

II.D.i–6
A Dosing Study of Nonoxynol–9 and Genital Irritation.
Author: Roddy, R. E.; Cordero, M.; Cordero, C.; Fortney, J. A.
[See abstract II.B.i–21.]

II.D.*ii.* Clinical Studies of Administration, Dosage, Delivery–Other.

II.D.ii–1
Vaginal Chlorhexidine Disinfection During Labour.
Author: Lindemann, R.; Henrichsen, T.; Svenningesen, L.; Hjelle, K.
[See abstract II.C.i.b–6.]

II.D.ii–2
The Effects of Frequent Nonoxynol–9 Use on the Vaginal and Cervical Mucosa.
Author: Niruthisard, S.; Roddy, R. E.; Chutivongse, S.
[See abstract II.B.i–17.]

II.D.ii–3
A Dosing Study of Nonoxynol–9 and Genital Irritation.
Author: Roddy, R. E.; Cordero, M.; Cordero, C.; Fortney, J. A.
[See abstract II.B.i–21.]

II.D.ii–4
Nonoxynol–9 Use, Genital Ulcers, and HIV Infection in a Cohort of Sex Workers.
Author: Weir, S. S.; Roddy, R. E.; Zekeng, L.; Feldblum, P. J.
[See abstract II.B.i–26.]

II.D.iii–1

Anal Human Papillomavirus Infection Among Homosexual and Bisexual Men: Prevalence of Type-Specific Infection and Association With Human Immunodeficiency Virus.

Form: Journal Article.
Author: Breese, P. L.; Judson, F. N.; Penley, K. A.; Douglas, J. M. Jr.
Source: Sexually Transmitted Diseases. 22(1):7–14, January–February 1995.
Published Abstract: Background and Objective: "High-risk" types of genital human papillomavirus (HPV) infections are associated with anogenital cancer. As these cancers occur more frequently in immunosuppressed individuals, we sought to better characterize type-specific prevalence, clinical spectrum, and risk factors for anal HPV infection among homosexual men. Study Design: Cross-sectional and follow-up study of 93 HIV-seropositive (HIV+) and 116 HIV-seronegative (HIV!) homosexual/bisexual men, with testing of anal swabs for HPV DNA by Virapap/Viratype assay. Results: Overall, 57 (61%) HIV+ and 20 (17%) HIV! men had anal HPV detected (P < .0001). HPV types 16/18 were most common, accounting for more than 50% of infections. Among HIV+ men, HPV prevalence increased with declining CD4 cell count: 33% with counts of more than 750, 56% with counts of 200 to 750, and 86% with counts less than 200 (P = .01). HPV infection was also associated with younger age and increasing numbers of lifetime sexual partners for all men. Most infections were subclinical, with clinically apparent infection (anal warts) accounting for 35% of infections in HIV! men, 33% in asymptomatic HIV+ men, and 52% in men with AIDS/ARC. For both HIV! and HIV+ men, rates of anal HPV detection (23% and 60%) were greater than those for the perianal area (5% and 37%) or penile shaft (2% and 7%) (P < .001). Persistence of anal HPV for 6 months was more common among men with AIDS/ARC (95%) than among asymptomatic HIV+ men (62%) or HIV! men (61%) (P < .05). Conclusions: Anal HPV infections are common in homosexual/bisexual men and have a strong relationship to HIV-associated immunosuppression. Because most infections involve "high-risk" types of HPV, studies of their natural history are needed to clarify the risk of anal neoplasia in men with HIV infection.

II.D.iii–2

Rectal Gonorrhoea as an Independent Risk Factor for HIV Infection in a Cohort of Homosexual Men.

Form: Journal Article.
Author: Craib, K. J.; Meddings, D. R.; Strathdee, S. A.; Hogg, R. S.; Montaner, J. S.; O'Shaughnessy, M. V.; Schechter, M. T.

Authors' Abstract: Objective: To determine whether certain sexually transmitted diseases (STDs) are independent risk factors for HIV transmission in a cohort of homosexual men. Methods: Eligible cases were identified as those who had seroconverted between November 1982 and November 1990. Two persistently HIV–seronegative control participants were randomly selected for each case from all participants who remained seronegative in November 1990. For cases, risk factor data were taken from an index visit which was defined as the first seropositive visit, while for controls these data were obtained from a matched visit which occurred within 2 months of the index visit for the corresponding case. Mantel–Haenszel methods and logistic regression were used to compare differences in risk factors for seroconversion between cases and controls. Results: A total of 125 cases and 250 controls were eligible for this study. Cases were significantly more likely to have had reported any gonorrhea (17% versus 6%; odds ratio (OR) = 2.94; 95% confidence interval (CI), 1.51–5.73) or syphilis (7% versus 2%; OR = 3.78; 95% CI, 1.33–10.79) than controls during the seroconversion period. Multivariate logistic regression revealed rectal gonorrhoea to be independently associated with risk of seroconversion (OR = 3.88; p = 0.044), whereas urethral gonorrhoea (p = 0.479) and pharyngeal gonorrhoea (p = 0.434) were not after inclusion of rectal gonorrhoea. In addition, the following variables were also shown to exert an independent effect on seroconversion: frequency of anal intercourse, use of illicit drugs, number of male sexual partners, and lack of a post–secondary education. Conclusions: In this observational study, rectal gonorrhoea was found to be associated with HIV seroconversion after adjustment for a number of HIV risk

factors. We cannot rule out that rectal gonorrhoea was not directly associated with HIV infection but rather with other residual lifestyle factors not fully adjusted for in the analysis. However, the relationship with gonococcal involvement of a specific anatomic site lends support to a biological association between gonorrhoea and HIV infection, rather than to alternative non–biologic explanations. Our findings are consistent with previous studies reporting an association between HIV infection and non–ulcerative STDs. Such a direct association might be explained by postulating that gonorrhoea results in inflamed rectal mucosa and compromised epithelial integrity, thereby predisposing an individual to subsequent HIV infection.

II.D.iii–3
Role of the Primary Infection in Epidemics of HIV Infection in Gay Cohorts.

Form: Journal Article.
Author: Jacquez, J. A.; Koopman, J.S.; Simon, C. P.; Longini, I. M. Jr.
Source: Journal of Acquired Immune Deficiency Syndromes. 7(11):1169–84, November 1994.

Authors' Abstract: A review of the data on infectivity per contact for transmission of the human immunodeficiency virus (HIV) suggests that the infectivity may be on the order of 0.1–0.3 per anal intercourse in the period of the initial infection, 10(!4) to 10(!3) in the long asymptomatic period, and 10(!3) to 10(!2) in the period leading into AIDS. The pattern of high contagiousness during the primary infection followed by a large drop in infectiousness may explain the pattern of epidemic spread seen in male homosexual cohorts in the early years of the epidemic. Simulations of cohorts of homosexual males, using that range of parameter values, indicate the following: (1) The initial fast rise and then more or less rapid flattening of the incidence curve of seropositives is primarily due to rapid initial spread, yielding a group of infecteds all of whom pass into the low infectivity asymptomatic period at close to the same time; all this occurs only if the basic reproduction number for the primary infection is >1. (2) The behavioral changes that have been reported all started after the incidence of new infections began to fall, too late to have a major effect on the initial rise; the behavioral changes had a major effect in slowing down the subsequent rise in the number of seropositives. (3) High activity groups play an important role in the early rapid rise of the epidemic; however, it is not likely that the rapid decrease in rate of growth of seropositives is solely due to saturation of these very high activity groups. Although the evidence for this interpretation of the role of the primary infection is not conclusive, its implications for prevention and for vaccine trials are so markedly different from those of other interpretations that we consider it to be an important hypothesis for further testing.

II.D.iii–4
T– and B–Cell Functions and Epitope Expression in Nonhuman Primates Immunized With Simian Immunodeficiency Virus Antigen by the Rectal Route.

Form: Journal Article.
Author: Lehner, T.; Brookes, R.; Panagiotidi, C.; Tao, L.; Klavinskis, L. S.; Walker, J.; Walker, P.; Ward, R.; Hussain, L.; Gearing, J. H.; et al.
Source: Proceedings of the National Academy of Sciences of the United States of America. 90(18):8638–42, September 15, 1993.

Authors' Abstract: Transmission of human immunodeficiency virus (HIV) in North America and Europe occurs most commonly through the rectal mucosa during homosexual intercourse. The simian immunodeficiency virus (SIV) macaque model has been used to investigate rectal immunization. The vaccine used was a recombinant SIV gag p27 expressed as hybrid Ty virus–like particles (Ty–VLP). Sequential ororectal (OR) mucosal immunization was compared with i.m. immunization. Whereas both routes of immunization induced serum IgA and IgG p27 antibodies, only OR immunization induced rectal secretory IgA antibodies. Specific CD4+ T–cell proliferative responses to stimulation with p27 were found after i.m. immunization only in the blood and spleen, but after OR immunization they were found in the internal iliac and inferior mesenteric lymph nodes in addition to the blood and spleen. T–cell epitope mapping of the proliferative responses of short–term cell lines (STCLs) grown from peripheral blood or lymphoid cells revealed a major epitope within the polypeptide 121–150 after either route of immunization. Two minor T–cell epitopes were found within peptide 41–80 in STLCs from splenic and circulating cells. B–cell epitope mapping of serum or biliary IgA

and IgG antibodies revealed two overlapping or adjacent immunodominant epitopes to the T–cell epitopes within the polypeptides 121–170 and 51–90. The results suggest that rectal augmented by oral immunization with a recombinant particulate antigen in nonhuman primates elicits secretory IgA and to a lesser extent IgG responses in the draining lymph nodes and the rectal mucosa, whereas systemic immunization targets predominantly splenic and circulating T– and B–cell responses. These findings may have important implications in the strategy of designing vaccines in prevention of homosexual transmission of HIV infection.

II.D.iii–5

Mucosal Model of Genital Immunization in Male Rhesus Macaques With a Recombinant Simian Immunodeficiency Virus p27 Antigen.

Form: Journal Article.
Author: Lehner, T.; Tao, L.; Panagiotidi, C.; Klavinskis, L. S.; Brookes, R.; Hussain, L.; Meyers, N.; Adams, S. E.; Gearing, A. J.; Bergmeier, L. A.
Source: Journal of Virology. 68(3):1624–32, March 1994.

Authors' Abstract: Human immunodeficiency virus (HIV) can be transmitted through infected seminal fluid or vaginal or rectal secretions during heterosexual or homosexual intercourse. To prevent mucosal transmission and spread to the regional lymph nodes, an effective vaccine may need to stimulate immune responses at the genitourinary mucosa. In this study, we have developed a mucosal model of genital immunization in male rhesus macaques, by topical urethral immunization with recombinant simian immunodeficiency virus p27gag, expressed as a hybrid Ty virus–like particle (Ty–VLP) and covalently linked to cholera toxin B subunit. This treatment was augmented by oral immunization with the same vaccine but with added killed cholera vibrios. Polymeric secretory immunoglobulin A (sIgA) and IgG antibodies to p27 were induced in urethral secretions, urine, and seminal fluid. This raises the possibility that the antibodies may function as a primary mucosal defense barrier against SIV (HIV) infection. The regional lymph nodes which constitute the genital–associated lymphoid tissue contained p27–specific CD4+ proliferative and helper T cells for antibody synthesis by B cells, which may function as a secondary immune barrier to infection. Blood and splenic lymphocytes also showed p27–sensitized CD4+ T cells and B cells in addition to serum IgG and IgA p27–specific antibodies; this constitutes a third level of immunity against dissemination of the virus. A comparison of genito–oral with recto–oral and intramuscular routes of immunization suggests that only genito–oral immunization elicits specific sIgA and IgG antibodies in the urine, urethra, and seminal fluid. Both genito–oral and recto–oral immunizations induced T–cell and B–cell immune responses in regional lymph nodes, with preferential IgA antibody synthesis. The mucosal route of immunization may prevent not only virus transmission through the genital mucosa but also dissemination and latency of the virus in the draining lymph nodes.

II.D.iii–6

Seroprevalence of HIV and Risk Behaviors Among Young Homosexual and Bisexual Men.

Form: Journal Article.
Author: Lemp, G. F.; Hirozawa, A. M.; Givertz, D.; Nieri, G. N.; Anderson, L.; Lindegren, M. L.; Janssen, R. S.; Katz, M.
Source: JAMA. 272(6):449–454, August 10, 1994.

Authors' Abstract: Objective: To estimate the prevalence of human immunodeficiency virus (HIV) infection and risk behaviors among young homosexual and bisexual men sampled from public venues in San Francisco and Berkeley, California. Design: A survey of 425 young homosexual and bisexual men sampled from 26 locations during 1992 and 1993. Participants were interviewed and blood specimens were drawn and tested for HIV, level of CD4+ T lymphocytes, and markers of hepatitis B and syphilis. Setting: Public venues of San Francisco and Berkeley, including street corners and sidewalks, dance clubs, bars, and parks. Population Studied: Homosexual and bisexual men aged 17 to 22 years. Main Outcome Measures: Prevalence of HIV infection and risk behaviors. Results: The HIV seroprevalence was 9.4% (95% confidence interval (CI), 6.8% to 12.6%). The prevalence of markers for hepatitis B was 19.8% (95% CI, 16.1% to 23.9%), and that for syphilis was 1.0% (95% CI, 0.3% to 2.4%). The HIV seroprevalence was significantly higher among African Americans (21.2%) than among other racial/ethnic groups (P = .002). Approximately one third (32.7%) of

the participants reported unprotected anal intercourse, and 11.8% reported injecting–drug use in the previous 6 months. At the time of the interview, 70.0% of the HIV–infected men did not know they were HIV seropositive, and only 22.5% were receiving medical care for HIV infection. Conclusions: The prevalence of HIV infection is high among this young population of homosexual and bisexual men, particularly among young African–American men. The high rates of HIV–related risk behaviors suggest a considerable risk for HIV transmission in this population. Prevention programs and health services need to be tailored to address the needs of a new generation of homosexual and bisexual men.

II.D.iii–7
Inappropriate Lubricant Use With Condoms by Homosexual Men.
Author: Martin, D. J.
[See abstract II.B.i–15.]

II.D.iii–8
Effect of Sexual Behavior Change on Long–Term Human Immunodeficiency Virus Prevalence Among Homosexual Men.

Form: Journal Article.
Author: Morris, M.; Dean, L.
Source: American Journal of Epidemiology. 140(3):217–232, August 1, 1994.

Authors' Abstract: Substantial changes in human immunodeficiency virus (HIV)–related sexual behavior have been reported by virtually every survey of homosexual/bisexual men in the last decade. This paper uses a behavior–based simulation to examine how such changes are likely to affect the long–term future of the acquired immunodeficiency syndrome (AIDS) epidemic among homosexual men. Data from the Longitudinal AIDS Impact Project in New York City are used to estimate age–specific patterns of unprotected anogenital contact and behavioral change from 1980 to 1991. Model projections are validated using New York City surveillance data on AIDS incidence from 1981 to 1991. The current levels of unsafe sex reported in the Longitudinal AIDS Impact Project are shown to be almost exactly on the epidemic threshold. If this behavior were maintained, HIV prevalence would slowly decline in the population, but with just one additional unsafe sexual partner per year HIV would instead become endemic, with seroprevalence of about 65% in the oldest group and about 25% in the youngest. Transmission dynamics in the youngest group are analyzed in detail. For this group, the assortative age–matching bias in partner selection patterns raises the unsafe behavior threshold slightly in the long run.

II.D.iii–9
Brokering: A Process for Establishing Long–Term and Stable Links With Gay Male Communities for Research and Public Health Education.

Form: Journal Article.
Author: Silvestre, A. J.
Source: AIDS Education & Prevention. 6(1):65–73, February 1994.

Authors' Abstract: The success of efforts to prevent continued transmission of the human immunodeficiency virus (HIV) and to increase compliance with HIV prophylactic interventions among homosexual and bisexual men will depend in part on health care professionals' understanding of and ability to establish linkages with these men. In order to recruit men into a research project and an educational program, staff at the Pitt Men's Study, an epidemiological investigation of HIV infection, developed a process described here as "brokering," which was based on community organizing and marketing principles. Brokering is a dynamic process by which researchers and public health professionals exchange goods and services with formal and informal leaders of the gay community in order to establish strong, long–term linkages. To date, this process yielded 2,989 homosexual and bisexual recruits into the study, which began in 1983. After 8 years, 79% of those still alive continue to return for follow–up. While recruitment techniques will need to vary from city to city, the importance of establishing linkages with the local indigenous leadership remains of major importance.

II.D.iii–10
Spermicides for Controlling the Spread of HIV.
Author: Voeller, B.
[See abstract II.B.i–23.]

II.D.iii–11

Relevance And Feasibility of Clinical Trials of Topical Virucides Designed for Rectal Administration Among U.S. Gay Men.

Form: Jounal Article.

Authors: Gross, M.[1]; Buchbinder, S.[2]; Celum, C.[3,4]; Critchlow, C.[4,5]; Heagerty, P.[5]; Seage, G. R.[1] and The HIV Network for Efficacy Trials (HIVNET). [1]Abt Associates, Inc., Cambridge, MA, [2]San Francisco Department of Public Health, CA; [3]Harborview Medical Center, Seattle, WA; [4]University of Washington, Seattle, WA; [5]Fred Hutchinson Cancer Research Center, Seattle, WA.

Source: Th.C.320, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Background*: Sexual lubricants are used widely by gay men (GM) in the United States for anal intercourse. Many of these products contain nonoxynol–9 (N–9)—a spermicide with anti-HIV properties in vitro—despite the unknown safety and efficacy of N–9. *Objective*: The purpose of this article was to assess behavioral and attitudinal factors related to the importance of clinical trials of topical virucides for rectal use ["rectal microbicides"(RM)] as well as the willingness of GM to enroll in safety and efficacy trials of N–9 products and efficacy trials of products without N–9. (Hypothetical trial designs presumed continued condom use.) *Method*: A total of 2,723 HIV-sero–negative GM who practiced receptive anal sex enrolled in a Vaccine Preparedness Study in 6 U.S. cities where they answered self-administered questionnaires on possible future RM safety and efficacy trials and participated in interviewer-administered interviews on their condom and lubricant use, sexual practices, and related topics for the 6–month period prior to the study. *Results*: There is a need for additional barriers; 44% of the men reported having unprotected receptive anal sex during the previous 6 months, and 17% reported at least one episode of condom failure. Regarding the use of lubricants (with or without N–9), 80% of the men reported using lubricants for anal sex at least 80% of the time. In addition, 75% of men who used lubricants sought brands that contained N–9, although only 5% thought N–9 by itself would protect them against HIV transmission. And 18% of the men specifically avoided lubricants that contained N–9. Overall, 20% of the men were definitely willing to participate in RM trials, 47% were probably willing, 25% were probably not willing, and 8% were definitely not willing. There were no marked differences in this distribution by type of trial (safety, N–9 efficacy, and non-N–9 efficacy). Although 75% of the men did not think N–9 by itself could prevent HIV transmission during anal sex, more than 66% of those men were definitely or probably willing to participate in an RM trial of N–9 efficacy. With a majority of men routinely using lubricants during anal sex, this practice was not associated with the interest in RM trials. Increased willingness was found (on bivariate analysis) among men who had more frequent receptive anal sex and, for safety trials only, among men who had more frequent, unprotected, receptive anal sex. *Conclusion*: Prevention methods that can serve as an adjunct to condoms are needed among GM. GM seek N–9 products despite their unknown safety and efficacy. High rates of willingness to participate in RM trials suggest that such trials are feasible.

II.D.iii–12

Microbicidal Gel to Prevent the Sexual Transmission of HIV.

Form: Journal Article

Author: Bergeron, M. G.[1]; Gagne, N.[1]; Gourde, P.[1]; Perron, S.[1]; Tremblay, M.[1]; Beauchamp, D.[1]; Juhasz, J.[2]; Desormeaux, A.[1] [1]Centre de Recherche en Infectiologie, Centre Hospitalier de l'Universite Laval, Ste-Foy, Quebec, Canada; [2]Ecole de Pharmacie, Universite Laval, Ste-Foy, Quebec, Canada.

[See Abstract I.H–20.]

III.A. Behavioral Studies–Acceptability.

III.A–1
A User Acceptability Study of Vaginal Spermicides in Combination With Barrier Methods or an Intrauterine Device.

Form: Journal Article.
Author: Black, C.; Houghton, V. P.
Source: Contraception. 28(2):103–110, 1983.
[See abstract II.B.ii–2.]

III.A–2
Clinical Acceptability, Use–Patterns and Use–Effectiveness of the Vaginal Contraceptive Sponge and Neo Sampoon Tablets: An International Multi–Center Randomized Clinical Trial.

Form: Journal Article.
Author: Chi, I. C.; Smith, S. C.; Borko, E.; Sun, T. H.; Begum, S. F.; Hunt, W. L.; Wilkens, L. R.
Source: Contraception. 36(5):499–514, November 1987.

Published Abstract: This paper describes the results from a randomized clinical trial comparing the Collatex® vaginal contraceptive sponge (a predecessor of the Today® sponge) with Neo Sampoon® foaming vaginal contraceptive tablets. The trial was conducted from 1979 to 1983 in four centers located in three countries (two centers in Yugoslavia, one in Taiwan, and one in Bangladesh). Clinically significant medical complications were rarely reported for either method. More insertion and retention problems were associated with the sponge than with the tablet, especially in the two Asian centers. Neo Sampoon® users complained of a burning or stinging sensation; however, this effect seemed to be well tolerated and was not a frequent reason for irregular and/or discontinuation of use of the tablets. Sponge users were more likely to report irregular use than tablet users, primarily due to the inconvenience of using the sponge. Rates of discontinuation after 6 months of use were also consistently higher among sponge users than among tablet users in the four centers. Life-table pregnancy rates after 12 months of use ranged from 3.8 to 18.2 per 100 Collatex® users and 6.2 to 29.9 per 100 Neo Sampoon® users, based on data from the two Yugoslavian centers and the Taiwanese center (data from the Bangladesh center were excluded from analysis of pregnancy rates). Practical implications of these findings are discussed.

III.A–3
User's Perspectives and Contraceptive Technology and Delivery Systems.

Form: Journal Article.
Author: Bruce, J.
Source: Journal of Technology in Society. 359–383, 1987.

Published Abstract: This paper presents a framework of feminist concerns through which to view the potential acceptability of new contraceptive technologies and family–planning service delivery systems. The framework was constructed using knowledge of the roles and status of women in developing countries—particularly the women's power relations—as well as acceptability and program research and selected, more theoretical feminist perspectives.

III.A–4
A Comparative Study of the Safety, Effectiveness, and Acceptability of Two Foaming Vaginal Tablets (Nonoxynol–9 vs. Menfegol) in Thai Women.

Form: Journal Article.
Author: Chompootaweep, S.; Dusitsin, N.
Source: Contraception. 41(5):507–517, May 1990.
[See abstract II.B.ii–3.]

III.A–5
Psychosocial Aspects of Contraception.

Form: Book Chapter.
Author: Clarke, L.
Source: Psychology and Gynecological Problems. (Annabel K. Broome, Louise Wallace, Eds.) London: Tavistock/Routledge, 1984.

Published Abstract: This chapter focuses on why people use contraception or other means to curtail their fertility and why some people do not

use contraception, have unwanted pregnancies, or use contraception inconsistently or incorrectly even if contraceptive methods are freely available. These are crucial questions, whether one's interest is the improvement of the quality of life for individuals or the problem of world overpopulation. Although the desire to control fertility and the means to achieve this desire are necessary preconditions for successful fertility regulation and contraceptive use, the relative importance of the psychosocial influences and the technology are debatable and are somewhat intertwined. This concept is examined through discussion of trends in contraceptive practice (including the contraceptive behavior of specific groups and the role of contraception); psychosocial influences on contraceptive use (such as the efficiency and acceptability of contraception, attributes of contraceptive methods, and attitudes about contraceptive use); explanatory theories of fertility–regulating behavior; and implications for contraceptive advice, education, and service delivery.

III.A–6
Traditional Vaginal Agents Use and Association With HIV Infection in Malawian Women.

Form: Journal Article.
Author: Dallabetta, G. A.; Miotti, P. G.; Chiphangwi, J. D.; Liomba, G.; Canner, J. K.; Saah, A. J.
Source: AIDS. 9(3):293–297, March 1995.

Published Abstract: The authors of this article assess the prevalence of traditional vaginal agent use in Malawian women and its association with human immunodeficiency virus (HIV) infection. Data from Africa show that intravaginal use of herbs or cloth to create a tightening effect ("dry sex") increased the risk of HIV seropositivity in women. Agents varied from herbs and a powder prepared from a variety of local leaves and plant stems to stones and aluminum hydroxide powder, which were used more frequently for self–treatment purposes. Consenting, antenatal women were administered a questionnaire and were screened for sexually transmitted diseases (STDs), including HIV. Of the 6,603 women studied, 886 (13%) reported using intravaginal agents for tightening and 2,222 (34%) reported using intravaginal agents for self–treatment of vaginal discharge and itching. A higher proportion of HIV–infected than uninfected women (17% versus 14%) reported use of intravaginal agents for treatment (odds ratio, 1.29; 95% confidence interval 1.05–1.57), but no difference in proportion was found when these agents were used for tightening. In multivariate analysis, use of vaginal agents for treatment was independently associated with HIV seropositivity. The association of HIV infection with vaginal agents used for self–treatment but not for tightening suggests that STDs may result from vaginal agent usage or that the agents are used differently for the two purposes. In addition to a small increased risk of HIV infection associated with vaginal agent use, these agents may interfere with condom effectiveness or acceptability of vaginal microbicides.

III.A–7
Risk Acceptability According to the Social Sciences.

Form: Report.
Author: Douglas, M.
Source: Social Research Perspectives: Occasional Reports on Current Topics, Vol. 11. New York: Russell Sage Foundation, 1985.

Published Abstract: The subject matter of this report focuses not on risks but on risk perception from the viewpoints of various social sciences. Topics discussed include the moral issues that make risk perception an important policy matter; the emergence of a new subdiscipline with origins in ecology, psychology, and economics that is dedicated to the perception of risk; psychology's approaches to risk perception and its tendency to neglect the social dimension; and how risk fits into the theory of choice. These topics move further and further away from real–world concerns and toward pure theory, but real–world concerns are revisited in a discussion of how moral judgment is involved with risk perception, even in present society. The remainder of this report concerns how perception of risks is encoded in social institutions; the goal is not to remonstrate, but rather to discuss an approach to risk perception that has not been tried before.

III.A–8
Gender–Specific Risk and Strategy for Behavior Change Among Women.

Form: Journal Article.
Author: Ehrhardt, A. A.; Exner, T.; Ortiz–Torres, B.; Yingling, S.; Zawadzki, R.
Source: HIV Infect Women Conf. p S27, February 22–24, 1995.

Published Abstract: A prevention program for women must be different than one for men because barriers to condom use differ between the sexes. Women do not control condom use and have considerably less power in sexual relations than men; therefore, prevention strategies for women need to focus on empowerment to negotiate and to refuse. Instead of women being trained to overcome their sexual inhibitions, they should be taught gender negotiation so they can overcome barriers to condom use. In addition, there is an urgent need for development of new methods that put women in control.
Microbicides/virucides are currently being developed, but they need to be tested for appropriate acceptability within the realities of women's lives. A female condom is being assessed and tested for acceptability. This article reports women's reactions to the introduction of the female condom and their effectiveness ratings and preferential choices of other female–controlled methods such as spermicides, the sponge, and the diaphragm as compared with the male condom. This article also discusses data from a new, primary prevention study of women attending a Family Planning Clinic in Brooklyn, New York. The study involved 100 women whose median age was 22 years; 62 women were African American, 34 were Latina, and 13 were Caucasian. The following risk profile emerged: 54% had an STD, only 26% reported consistently using condoms during vaginal intercourse, and 60% either doubted their male partner's monogamy or knew of other partners. Physical abuse by male partners was high; 46% of the women reported that they had been physically abused, 30% reported being sexually abused, and 21% were physically abused by their current male partner.

III.A–9
Contraceptive Efficacy and Acceptability of the Female Condom.

Form: Journal Article.
Author: Farr, G.; Gabelnick, H.; Sturgen, K.; Dorflinger, L.
Source: American Journal of Public Health. 84(12):1960–1964, December 1994.

Published Abstract: *Objectives*: The purpose of this study was to determine the contraceptive efficacy of the female condom and to provide data about the device to the U.S. Food and Drug Administration. *Methods*: The clinical trial was conducted at nine sites—six in the United States and three in Latin America. Eligible subjects were in mutually monogamous relationships and agreed to use the female condom as their only means of contraception for 6 months. *Results*: A total of 328 subjects contributed to the analysis of contraceptive efficacy of female condoms. Twenty-two U.S. subjects and 17 Latin American subjects became pregnant, yielding gross accidental pregnancy rates over a 6–month cumulative period of 12.4% and 22.2%, respectively. However, during perfect (consistent and correct) use of the device, the 6-month accidental pregnancy rates were 2.6% and 9.5% for the U.S. and Latin American centers, respectively. There were no serious adverse events related to the use of the device. *Conclusions*: The female condom provides contraceptive efficacy in the same range as other barrier methods, particularly when used consistently and correctly, and it has an added advantage of helping to protect against sexually transmitted diseases.

III.A–10
Women–Centered Prevention Techniques and Technologies.

Form: Book Chapter.
Author: Gollub, E. L.
Source: Women at Risk: Issues in the Primary Prevention of AIDS. AIDS Prevention and Mental Health. (Ann O'Leary, Loretta Sweet Jemmott, Eds.) New York: Plenum Press, 1995.

Published Abstract: This chapter reviews data pertaining to barrier methods and other protective strategies for prevention of AIDS that are now available for women. Although contraception is probably not necessary for AIDS prevention, all current barrier methods are contraceptives. This overlap has posed an important obstacle to many women worldwide—they are unable to conceive while practicing prevention of AIDS and other sexually transmitted diseases (STDs). This chapter

discusses issues on the effectiveness and acceptability of various physical and chemical barriers that have demonstrated an ability to reduce the risk of sexually transmitted infections such as chlamydia and gonorrhea. It also mentions practices that may increase women's vulnerability to HIV and other sexually transmitted organisms. A summary of research areas for the future includes the issue of currently unavailable "microbicide" as well as the issue of integrating STD prevention and family planning services into an approach to women's reproductive health care needs. There is also an appeal for solidarity among women of all disciplines and backgrounds who are working to put an end to the epidemic of STDs.

III.A–11
Explaining Choices Among Technological Risks.

Form: Journal Article.
Author: Clarke, L.
Source: Social Problems. 35(1):22–35, February 1988.

Published Abstract: This article discusses the process of defining some risks as acceptable. The predominant view—one that is based on psychological research—is summarized and then criticized for its insufficient consideration of the structural context within which decisions about risks are made. To develop a more sociological perspective on acceptable risk, evidence is presented concerning choices made in nuclear power, the unsafe Ford Pintos, and an instance of toxic chemical contamination. The analysis is grounded in organizational theory and centers on decision–making processes regarding technological risks. It is argued that although risk acceptability has traditionally been seen as a political issue, a scientific risk assessment often involves factors that result from intergroup conflict.

III.A–12
AIDS Prevention and Education: Reframing the Message.

Form: Journal Article.
Author: Citizens Commission on AIDS for New York City and Northern New Jersey.
Source: AIDS Education and Prevention. 3(2):147–163, Summer 1991.

Published Abstract: This article discusses the prevention of human immunodeficiency virus (HIV) infection, which can be furthered through education directed at the general public, at communities and small groups, and at individuals and their sexual and drug–using partners. The social climate in which risk–reduction messages are communicated is an important factor in the acceptability of the messages. Therefore, the stigma and discrimination surrounding acquired immunodeficiency syndrome (AIDS) must be eliminated because of the resultant injustices and because negative attitudes and actions deter prevention efforts. In addition, the stigma of AIDS may cause those who engage in risky behavior to deny their risk and to avoid counseling and other educational efforts. Recommendations are made concerning the role of the government, mass media, workplaces, educational institutions, and foundations in bringing about needed changes. A list of 10 myths about AIDS education is also presented.

III.A–13
Acceptability Studies of Modern Methods of Fertility.

Form: Symposium and Conference Presentations: 81–33308.
Author: David, H. P.
Source: Reproductive rights and reproductive behavior: Clash or convergence of private values and public policies? 101st Annual Conference of the American Psychological Association Distinguished Contribution to the International Advancement of Psychology Award Address (1993, Toronto, Canada).
Source: American Psychologist. 49(4):343–349, April 1994.

Published Abstract: Using a rational, scientific approach that upholds public health values, this article examines the information gained from 25 years of cooperative transnational research on reproductive behavior. An overview of world population trends is followed by discussions of the human right to reproduce and the use of acceptability studies concerning modern methods of fertility regulation. Findings from research on psychological responses to abortion, long–term developmental effects of compulsory pregnancies, and the use of incentives and disincentives to influence family size are also discussed. In addition, there is

consideration of the clash between private values and public policy on reproductive behavior in the United States and consideration of the convergence achieved in Denmark and the Netherlands, where rates of unintended pregnancy are among the world's lowest.

III.A–14
Female–Controlled Methods To Prevent Sexual Transmission of HIV.

Form: Journal Article.
Author: Elias, C.; Coggins, C.
Source: AIDS. 10(3):543–551, 1996.

Published Abstract: Women throughout the world face a growing risk of infection with HIV. Consistent condom use, which is one cornerstone of primary prevention strategy, is not always feasible for many women. Consequently, women urgently need infection prevention technology that is within their personal control. This article reviews current efforts to develop and test female–controlled methods for preventing sexual transmission of HIV and other pathogens. Both physical and chemical methods of prevention are summarized, including recent findings on the efficacy and acceptability of the vaginal pouch (female condom) as well as an overview of research on vaginal microbicides. Data from studies of existing, over–the–counter spermicides are reviewed. The wide range of new microbicidal products currently being evaluated in laboratories and through early clinical trials demonstrates the breadth of possibility presented by chemical barrier methods. However, formidable challenges face public– and private–sector research and development efforts. This article concludes by highlighting several issues related to the introduction and clinical evaluation of female–controlled prevention technology.

III.A–15
Challenges for the Development of Female–Controlled Vaginal Microbicides.

Form: Journal Article.
Author: Elias, C. J.; Heise, L. L.
Source: AIDS. 8(1):1–9, January 1994.

Published Abstract: None.
Annotators' Abstract: The authors make general points about microbicide development. The development and testing of safe, effective, and affordable microbicidal products for women at risk for human immunodeficiency virus (HIV) infection raise complex scientific, ethical, and political issues. A range of products (gels, foams, suppositories) that protect against HIV and other sexually transmitted diseases without impairing conception would be ideal. The authors discuss the difficulty of conducting a Phase III effectiveness trial that would distribute the burdens and benefits of research equitably and provide controls with an alternative means of protection against HIV while maintaining scientific rigor. Since clinical trials call for a study population with a high seroincidence rate attributable primarily to the sexual transmission of HIV, prostitutes would be the logical choice of subjects; sex workers are, however, the women most vulnerable to physical and economic exploitation. Women's input will be essential at each stage of development and testing, providing valuable feedback on methods of application and timing of insertion. Finally, public–sector organizations must assume leadership in coordinating the development of HIV–prevention technologies.

III.A–16
Spermicides and Barrier Contraception.

Form: Journal Article.
Author: Faundes, A.; Elias, C.; Coggins, C.
Source: Current Opinion in Obstetrics and Gynecology. 6(6):552–558, December 1994.

Published Abstract: The failure rate of condoms varies from 2% to 13% depending on the study population, yet condoms are the contraceptive method with the greatest capacity to protect against sexually transmitted diseases (STDs) and AIDS. Breakage and slippage during intercourse are important causes of condom failure, and individual behavior leading to consistent and correct use of condoms is the most important factor in their effectiveness. Female–controlled barrier methods may actually prevent more STDs than condoms because they are used more consistently. One study found that the use of a diaphragm continuously and without spermicide was well accepted and effective in preventing pregnancy. The female condom appears to have a contraceptive effectiveness close to that of other vaginal methods; it is likely that it also protects against STDs and AIDS. Nonoxynol–9 appears to have

a protective effect against some STDs. Although data concerning how spermicides with nonoxynol–9 protect against HIV are conflicting, they suggest some protection, especially if products are used with relatively low frequency to avoid dose–dependent vaginal irritation. New spermicides that could protect against viral infection without affecting epithelial cells are currently being studied.

III.A–17

The Needs of Women: Conflicting Views of Safety and Acceptability of Contraceptive Policy Makers and Researchers vs. the Interest of Family Planning Personnel.

Form: Journal Article.
Author: Hardin, A.
Source: Social Science Medicine. 35(6):753–766, 1992.

Published Abstract: After having contributed significantly to women's liberation in the 1960s, contraceptives became increasingly subject to criticisms in the 1970s and 1980s. Feminist health groups point out the health risks of contraceptives and advocate barrier methods that do not interfere with complex body functions. The safety issues raised concern both the working mechanisms of the new technologies and the manner in which the technologies are used in family planning programs. Against this background, the author argues that much of the criticism from women's health advocates concerning the safety and acceptability of new contraceptive technologies has to do with the standard medical practice of developing and evaluating the technologies. This process is not sufficiently oriented toward women's reproductive needs, their experiences in using the methods, and the health care infrastructure in which the methods are to be provided. This is illustrated with case material on Depo Provera (a hormonal injection), Norplant (a hormonal implant), the abortion pill, and the contraceptive vaccine as well as with a review of acceptability trials of Norplant.

The author argues that women's perspectives and needs should be taken into consideration in the design and interpretation of controlled clinical and acceptability trials. Each potential new contraceptive technology should be subjected to a "technology assessment." In such an assessment, short– and long–term social consequences of the technology's application could be studied. Although technology assessment is used extensively to study new medical technologies, it does not seem to have been used systematically to assess the appropriateness of new contraceptive technologies. The author concludes the article by pointing out that methodologies for the incorporation of women's perspectives into contraceptive development and the technology assessment process still need to be developed. Such methodologies should acknowledge the differences in perspective and needs of women in different societal and cultural settings.

III.A–18

Spermicide Acceptability Among Patients at a Sexually Transmitted Disease Clinic in Zambia.

Form: Journal Article.
Author: Hira, S. K.; Spruyt, A. B.; Feldblum, P. J.; Sunkutu, M. R.; Glover, L. H.; Steiner, M. J.
Source: American Journal of Public Health. 85(8):1098–1103, August 1995.

Published Abstract: This study assessed the acceptability of three nonoxynol–9 spermicides among persons attending a sexually transmitted disease (STD) clinic in Lusaka, Zambia. Foam (100 mg, 12.5%), suppositories (100 mg, 5.56%), and tablets (100 mg of nonoxynol–9) were evaluated. Each of the 114 women and 150 men enrolled in the study used 2 products for 2 weeks. Consistency of use and acceptability were then evaluated. Most of the women (74%) and more than half of the men (58%) were not using any family planning method at the time of the study. In addition, the majority of participants (85% of women and 98% of men) had at least one STD or a genital infection. During the study, the proportion of coital episodes protected by spermicide use was high, yet loss to followup and discontinuation of use was also substantial. Discontinuation of use was frequently unrelated to acceptability but was instead related to personal reasons. Improved sexual satisfaction was the most frequently reported best feature, followed by convenience and prevention of pregnancy and STDs. Foam was the least desirable method of spermicide delivery. The results of this study suggest that it is feasible to distribute spermicides to women and men who are at increased risk for STDs, and that the products will be used. The authors call for further research to be done in different populations.

III.A–19
Risk Perception and Communication.

Form: Journal Article.
Author: Fischhoff, B.; Bostrom, A.; Quadrel, M. J.
Source: Annual Review of Public Health. 14:183–203, 1993.

Annotators' Abstract: This review article discusses some aspects of how people make decisions about risk. A study by Lichenstein et al. of subjects who were asked to rate 30 major causes of death is discussed. Issues were internal consistency, anchoring bias, compression (overestimating small frequencies and underestimating large ones), availability bias, miscalibration of confidence judgments (inadequate sensitivity to the extent of one's knowledge) and verbal quantifiers were identified to assist with the latter, perceived lethality, and perceived invulnerability. They were also asked to define catastrophic potential, dimensions of risk, and risk comparison. The article reviews perspectives on cumulative risk and potential mental processes involved with risk processes.

III.A–20
Recommendations for the Development of Vaginal Microbicides.

Form: Journal Article.
Author: The International Working Group on Vaginal Microbicides.
Source: AIDS: Special Report. 10, 1996.

Published Abstract: Vaginal microbicides are products for vaginal administration that can be used to prevent human immunodeficiency virus (HIV) infection and other sexually transmitted diseases (STDs). The potential sources for vaginal microbicides are existing spermicides and new products that may or may not be spermicidal. This document is a general guide for the development and evaluation of existing and new products. For example, preclinical studies will be required for new products. In addition, spermicides should be assessed according to their indications, in vitro activity against HIV, and the STDs they target. Other guidelines to use in the development of microbicides include evaluating the compatibility between microbicides and barrier method materials, assessing the physical and chemical properties of the active agents and the clinical formulations, conducting animal studies to assess microbicide safety and to predict dosing, and using various models to assess local toxicity and microbicidal activity of the products (if appropriate models are available). Carcinogenicity testing and segment II reproduction studies (perinatal and postnatal studies in rats) may be performed concurrently with Phase II clinical trials. All vaginal microbicides, including existing spermicides and new products, should be clinically evaluated for safety and efficacy. Safety studies are necessary because irritation of vaginal and cervical mucosae has been associated with spermicide use, and resultant lesions may increase HIV transmission. Efficacy studies should then be conducted on products that have been evaluated for safety and appear to be nontoxic to tissue; these studies should assess prevention of HIV infection and/or STDs, depending on the product indications. For spermicidal microbicides, contraceptive efficacy studies will be needed.

III.A–21
Contraceptive Acceptability Research: Utility and Limitations.

Form: Journal Article.
Author: Keller, A.
Source: Studies in Family Planning. 10(8–9):230–237, August–September 1979.

Published Abstract: Acceptability studies that employ attitudinal and/or behavioral variables have resulted in semantic controversies and confusion. This article reviews the limits of acceptability studies using Mexican attitudinal studies as examples. Mexican attitudinal studies are classified according to three types: hypothetical methods and attributes of methods, methods in clinical trials, and culturally based attitudes. In two studies of family planning and method attitudes, fears of infidelity and female liberation were voiced in a group session but not in survey questions designed to evoke those fears. Attitudes ascertained were partially a function of the methodology employed. Behavioral studies are limited because they depict acceptability under special, not normal, circumstances—for example, through free sample studies, comparative field trials, and free choice studies. Prediction is justifiable only if study conditions remain unchanged in the real

world; therefore, attitudinal studies are better used to understand the reasons for people's evaluations instead of to predict acceptability.

III.A–22
Minority Women and Sexual Choice in the Age of AIDS.

Form: Journal Article.
Author: Kline, A.; Kline, E.; Oken, E.
Source: Social Science Medicine. 23(4):448–457, 1992.

Published Abstract: As rates of HIV infection among women continue to rise, health education efforts promoting safer sexual practices are increasingly targeting the female population. However, the wisdom of these efforts is often questioned on the grounds that women—especially disadvantaged, minority women—lack the necessary power in their relationships with men to influence the course of sexual decision–making. Using a qualitative, focus group methodology, the study explored the bases of sexual decision–making among groups of high–risk African–American and Hispanic women. A total of 134 women recruited from drug treatment centers and community agencies in 3 Northern New Jersey cities were separated into 16 focus groups. The breakdown of the 16 focus groups was as follows: 3 groups contained African–American intravenous (IV) drug users, 3 groups contained Hispanic IV drug users, 3 groups contained African–American HIV–positive women, 3 groups contained Hispanic HIV–positive women, 2 groups contained African–American sex partners of IV drug users, and 2 groups contained Hispanic sex partners of IV drug users. Findings suggest that minority women often retain substantial power in relation to their male partners with respect to sexual decision–making. Factors relating to perceptions of risk are frequently more salient barriers to the practice of safer sex in this population.

III.A–23
Perceived Acceptability of Risk Analysis as a Decision–Making Approach.

Form: Journal Article.
Author: MacGregor, D.; Slovic, P.
Source: Risk Analysis. 6(2):245–256, June 1986.

Published Abstract: Five hundred and forty subjects evaluated three methods for making a consumer product safety decision using scales relating to perceived acceptability, logical soundness, completeness, and sensitivity to moral and ethical concerns. Two of the methods were formalized techniques: cost–benefit analysis and risk analysis. The third method involved abiding by standard industry practices. Other factors in the decision–making context were also varied. Results indicate that formalized techniques were preferred over the standard practices method. Within the formalized methods, cost–benefit analysis was judged to be less acceptable than a comparable method that did not involve making explicit value tradeoffs. All methods were judged more acceptable when they led to improved product safety. Knowledge of consequences did not exert direct effect on judgments, although it interacted significantly with other variables.

III.A–24
On the Acceptability of Different Methods of Family Planning in India: 1971–1980.

Form: Journal Article.
Author: Pathak, K. B.; Murthy, P. K.
Source: Indian Journal of Social Work. 44(4):393–403, January 1984.

Published Abstract: This article used affinity and distance indices to assess the acceptance of various family planning methods among Indian adults ages 20–29 years and 30–39 years in various States of India from 1974 to 1980. Results show that there is slow progress in the acceptance of sterilization and an increased demand for methods used by females, including tubectomies , birth–control pills, and intrauterine devices. Comparisons among various regions of India are also discussed.

III.A–25
Multicountry Study of Acceptability of Spermicidally Lubricated Condoms. IV International Conference on AIDS; Stockholm, Sweden; June 12–16, 1988.

Form: Conference Proceedings.
Author: Potter, L.; Williamson, N.; Clarke, K.
Source: Washington, D.C.: BioData Publishers, 1988.

Published Abstract: The purpose of the study was to determine if spermicidally lubricated condoms would be acceptable to men who currently use condoms and their male partners. Two brands of spermicidally lubricated condoms were tested in five countries: Bangladesh, Egypt, Ghana, Honduras, and Mali. Half of the participants received the Prime® condom lubricated with a 6.6% solution of nonoxynol–9 and half received the Double–S® condom, which was similarly lubricated but had extra spermicide in the tip. Participants evaluated the condoms after 1 month of use. A total of 633 men (51% using Prime®, 49% using Double–S®) participated; 85% of Prime® users and 76% of Double–S® users said they preferred the test condom over their regular brand. Although 17% of Double–S® users reported irritation or excess lubrication, all reported experiencing less slippage and breakage than with their usual brands. Partners' reactions were also positive. The authors therefore claim that spermicidally lubricated condoms are acceptable to this population of men who have sex with men.

III.A–26
Virucides in Prevention of HIV Infection. Research Priorities. World Health Organization Working Group on Virucides.

Form: Journal Article.
Author: Rosenberg, M. J.; Holmes, K. K.
Source: Sexually Transmitted Diseases. 20(1):41–44, January–February 1993.

Published Abstract: Vaginal spermicides have microbicidal properties that suggest their usefulness in protecting against the human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs). This notion is supported by laboratory, animal, and clinical investigations. Because of the importance of identifying additional methods of protection against these infections, better information is needed on female–controlled contraceptive methods. A consistent set of laboratory standards is needed to evaluate the in vitro activity of existing and future virucides. In addition, further evaluation of areas such as the actions of virucides and vehicles on different anatomical sites are needed, as well as evaluation of safety studies to judge the determinants of toxicity. Clinical studies might compare the efficacy of spermicides and condoms in preventing HIV and other STDs and might investigate psychosocial considerations that determine suitable candidates for vaginal virucides, how virucides are used, and how their use might be improved.

III.A–27
Assessment of a New, Modified Soft Jelly Capsule Containing Nonoxynol as Spermicide Contraceptive.

Form: Journal Article.
Author: Recio, R.; Bassol, S.
Source: Advances in Contraception. 8(1):51–55, March 1992.
[See abstract II.D.i–5.]

III.A–28
The Psychology of Contraceptive Surprises: Cumulative Risk and Contraceptive Effectiveness.

Form: Journal Article.
Author: Shaklee, H.; Fischhoff, B.
Source: Journal of Applied Social Psychology. 20(5):385–403, 1990.

Published Abstract: Two studies investigated young adults' expectations about long–term contraceptive effectiveness. Subjects were told about five hypothetical methods of contraception that varied in reported effectiveness, which was expressed in terms of the likelihood of avoiding pregnancy for a base period of 1 year (Experiment 1), 5 years, or 10 years (Experiment 2) of use. For each contraceptive method, subjects estimated the likelihood that a woman would avoid pregnancy while using the method for periods ranging from 2 months to 15 years, and then they rated how satisfied they would be with the method. For nearly half of the subjects, estimates of cumulative effectiveness did not decline as time periods increased. Those subjects who did realize that cumulative effectiveness declined over time estimated rates that decreased too slowly for methods of modest and low reliability and that were too similar to methods differing in effectiveness. Subjects were overly optimistic about effectiveness for time periods longer than the base period, and they were overly pessimistic about effectiveness for shorter time periods. Not surprisingly, given these results, subjects expressed more satisfaction when a method's effectiveness was expressed in shorter base periods. Such faulty understanding

of the long–term implications of contraceptive effectiveness may undermine people's ability to make informed contraceptive choices.

III.A–29
The Acceptability of the Female Condom Among Low–Income African–American Women.

Form: Journal Article.
Author: Shervington, D. O.
Source: Journal of the National Medical Association. 85(5):341–347, May 1993.

Published Abstract: Focus groups of African–American women [10 subjects with high social and educational status, 20 subjects (ages 14–65 years) with low–to–middle incomes, and 15 subjects (ages 17–53 years) with low incomes] discussed reproductive knowledge, attitudes, and practices and were then given experiential and educational information about the female condom. Although most subjects were aware of HIV and the value of the male condom, they did not perceive themselves to be at high risk and therefore engaged in unprotected sex. Fear of relationship loss was more operant in the health beliefs and actions of the majority of subjects than fear of contracting HIV. Subjects enthusiastically endorsed the female condom because they felt it would give them control over safe–sex practices without having to challenge the power of their male partners. [Note: Several typographical errors appear in this journal article. Corrections to these errors appear in the Journal of the National Medical Association, 85(7):497, 564.]

III.A–30
A Retrospective Clinical Study of a Vaginal Contraceptive Suppository.

Form: Journal Article.
Author: Squire, J. J.; Berger, G. S.; Keith, L.
Source: The Journal of Reproductive Medicine. 22(6):319–323, June 1979.

Published Abstract: None.
Annotators' Abstract: The authors evaluated the use of Semicid®, a vaginal contraceptive suppository containing the spermicide nonoxynol–9. The study was a retrospective review of 326 patient records. The subjects were instructed on the correct insertion technique and were asked to return regularly for followup examination. Most of the women (89%) reported that they used no other contraceptive method during the study period. After 24 months, the pregnancy rate was 0.3 per 100 women. The 2–year contraceptive continuation rate for all of the women was 80%. In a subgroup of 107 previously pregnant women ages 18–35 years who reported using no adjunctive contraceptive method during the study, the contraceptive continuation rate was 73.9%. The study demonstrated that the Semicid® suppository was a reliable and satisfactory contraceptive for the population of women evaluated.

III.A–31
Acceptability of Spermicidal Film and Foaming Tablets Among Women in Three Countries.

Form: Journal Article.
Author: Steiner, M.; Spruyt, A.; Joanis, C.; Glover, L.; Cordero, M.; Alvarado, G.; Onoka, C.
Source: International Family Planning Perspectives. 21:104, 1995.

Published Abstract: A convenience sample of 162 family planning clients in Kenya, the Dominican Republic, and Mexico provided data for an evaluation of the acceptability of two female–controlled contraceptive methods that may also provide disease protection. Women significantly preferred contraceptive film over foaming tablets at two sites. In Kenya, 86% of participants said they would rather use the film versus 14% who would rather use the tablets; in Mexico, these proportions were 58% and 30%, respectively. Although a slight majority of women in the Dominican Republic also preferred the film, about one–half of the participants there and in Mexico complained that the film sometimes stuck to their fingers during insertion.

III.A–32
Acceptability of Dual Method.

Author: Steiner, M.; Joanis, C.
Source: Family Planning Perspective. 25(5):234, September–October 1993.

Published Abstract: None.
Annotators' Abstract: The authors respond to

three articles that address concurrent use of condoms and spermicides. They focus on the potential negative effects of prescribing two methods, including increased cost and the likelihood that each method may be less conscientiously used than a single method. The authors cite data from a multisite study of concurrent condom and spermicide use. Use of at least one method was high at all three sites, but the use of both methods ranged from 75% of all coital episodes in Mexico to 43% in Kenya and to 4% in the Dominican Republic. The authors call for more research on the interactions between dual method use and method acceptability.

III.A–33
Measuring Contraceptive Effectiveness: A Conceptual Framework.

Form: Journal Article.
Author: Steiner, M.; Dominik, R.; Trussell, J. S.; Hertzpicciotto, I.
Source: Obstetrics and Gynecology. 88(3):S24–S30, September 1996.

Published Abstract: This article presents a conceptual model that outlines four measures of how well a contraceptive method works: efficacy, effectiveness, perfect–use pregnancy rate, and typical–use pregnancy rate. It also illustrates how four variables influence these measures; the variables are the capacity to conceive, frequency and timing of intercourse, degree of compliance, and inherent protection of the method. Because of interindividual as well as intraindividual variability of the first three variables, generalizing results from a contraceptive clinical trial and relating them to other populations is problematic. There is a hierarchy of generalizability of the four outcome measures, with the typical–use pregnancy rate the least generalizable but the easiest to measure, and efficacy the most generalizable but the hardest to measure. These four variables should be considered in the design and analysis of future contraceptive clinical trials. Finally, this article illustrates why the terms “pregnancy rate” and “failure rate” are not synonymous and why the latter term is not recommended for use.

III.A–34
Vaginal Microbicides for Preventing the Sexual Transmission of HIV.

Form: Journal Article.
Author: Stone, A.; Hitchcock, P. J.
Source: AIDS. 8(1):S285–S293, 1994.

Annotators’ Abstract: The authors of this article review the advantages, disadvantages, and characteristics of microbicides. In addition, they discuss potential mechanisms of action for candidate microbicides as well as clinical, epidemiological, and behavioral studies necessary to evaluate those components. Finally, they summarize additional research that is needed. They conclude that development of effective barrier products is a global priority that will require governments, nongovernmental organizations, industries, and research institutions to work to support and coordinate efforts.

III.A–35
AIDS Knowledge, Perceived Risk, and Prevention Among Adolescent Clients of a Family Planning Clinic.

Form: Journal Article.
Author: Weisman, C. S.; Nathanson, C. A.; Ensminger, M.; Teitelbaum, M. A.; Robinson, J. C.; Plichta, S.
Source: Family Planning Perspectives. 21(5):213–217, September–October 1989.

Published Abstract: A survey was conducted that measured acquired immunodeficiency syndrome (AIDS) knowledge, perceived risk, and prevention among 404 sexually active adolescent women who were patients of family planning clinics in Baltimore, Maryland. Results indicated that knowledge about AIDS was high; the average respondent answered seven out of nine questions correctly. Slightly more than half of the teenagers reported some degree of perceived risk of acquiring AIDS. However, perceived AIDS risk was not predictive of condom use during intercourse; the strongest predictor of condom use was having asked a partner to use one. This suggests that adolescent women may exert a greater influence on condom use than has been previously assumed. The authors recommend that AIDS prevention programs become more personalized and integrated into family planning programs. In addition, they suggest that adolescent clients should be advised to use condoms with spermicides and should be counseled in negotiating condom use with their

partners.

III.A–36
Barrier Contraceptives and Spermicides: Their Role in Family Planning Care.

Form: Manual.
Author: World Health Organization.
Source: Geneva, Switzerland; World Health Organization, 1987.

Published Abstract: None.
Annotators' Abstract: This manual on barrier contraceptives and spermicides discusses their effectiveness, advantages (including noncontraceptive), disadvantages, uses in special cases, family program considerations, supply logistics, monitoring of shelf life, quality control, and condom use in acquired immunodeficiency syndrome (AIDS) prevention programs. Condoms and foaming tablets are considered the most suitable contraceptives for developing countries, especially those in the Tropics. An appendix comprises basic information about AIDS and the relevance of barrier contraceptives and spermicides, as well as monogamy and abstinence, in preventing the transmission of AIDS.

III.A–37
A Practical Method To Reduce HIV Risk in African Women.

Form: Journal Article, Letter.
Author: Ziegler, J. L.
Source: Tropical Doctor. 24(4):189, October 1994.

Published Abstract: None.
Annotators' Abstract: The author makes three points about the need for female–controlled methods to prevent HIV: (1) Issues of safety, efficacy, compliance, and product liability will discourage commercial development. (2) Women who wish to become pregnant will not use anything with spermicidal activity. For widespread use in developing countries, vaginal microbicides would have to be inexpensive, readily available, easy to use, and aesthetically acceptable. (3) Postcoital douches with a locally prepared solution may be more practical than continuous prophylaxis. Because the practice of douching is event–related, compliance might improve. Douching is also more culturally acceptable than continuous prophylaxis; traditional healers have often prescribed herbal douches and enemas. The ideal preparation should be acidic (low pH), nonirritating, and microbicidal or virucidal. Possibilities include herbal tea (has low pH and tannins), locally brewed beer (has low pH, alcohol, and dextrans), sour milk (contains lactobacilli), and hypertonic saline.

III.A–38
Development of Vaginal Microbicides by the CONRAD Program: A Collaborative Effort for Research and Product Development.

Form: Journal Article.
Author: Claypool, L. E.; Krause, P. CONRAD Program, Arlington, VA, U.S.A.
Source: Th.C.4501, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Issue*: Microbicides that protect against HIV/AIDS and/or pregnancy and other STDs are urgently needed—especially those that can be used by women at their own discretion or when other barriers cannot be successfully used. New and better products may also contribute to greater acceptability and to more effective use of vaginal methods of protection. The effective development of new products requires fundamental information regarding biological transmissions and a rational plan for the evaluation of potential product leads. *Project*: The Contraceptive Research and Development (CONRAD) program, under a cooperative agreement with the U.S. Agency for International Development, supports extramural investigators in developing effective, safe, and acceptable contraceptive methods that are suitable for use in developing countries. CONRAD also pursues key objectives related to contraception and HIV/AIDS prevention with interagency funding from the National Institutes of Health (Contraceptive Development Branch, NICHE; S. D. Branch, NIAID) and Centers for Disease Control and Prevention, Division of Reproductive Health as well as with direct grants from the Mellon and Rockefeller Foundations. These objectives include 1) investigating new microbicidal agents and formulations, 2) investigating the physiology of sexual HIV transmission, 3) investigating animal models for genital HIV transmission, 4) investigating the activity of agents against other STDs, 5) studying epidemiological relationships between contraception and disease incidence,

6) conducting clinical trials, 7) developing a screening and decision plan for product development, and 8) conducting and publishing international workshops and fora to review progress. *Results*: Following competitive peer review, 41 subprojects have been supported with 25 principal investigators at universities, institutes, and private companies worldwide, resulting in 94 publications, 90 abstracts, and 2 workshop proceeding since 1988. Currently, structure/function and/or formulation and toxicology studies are under way for lead microbicidal agents; an in vivo model of genital HIV transmission using SIV and the rhesus macaque has been established and used for product evaluation; a detailed and prioritized sequence of testing and development activities has been collaboratively defined; and a new consortium has been established to stimulate private–sector interest and provide matching funds to not–for–profit institutions. *Lessons Learned*: This collaboration of public and private agencies is a cost effective and productive mechanism for supporting microbicide development.

III.A–39
Women's Protection From HIV/STD Infection Beyond the Male Condom.

Form: Journal Article.
Author: Ehrhardt, A. A.; Exner, T. M.; Hoffman, S.; Loeb, I. HIV Center for Clinical and Behavioral Studies, NYS Psychiatric Institute/Columbia University, New York, NY, U.S.A.
Source: Th.C.4500, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: The purpose of this article was to document women's experiences, practices, and reasons for adopting various strategies—including the male condom, female–controlled methods, and sexual practices—for protection against HIV and other STDs. *Methods*: Young women clients (ages 18–30 years) from a family planning clinic in a high–sero–prevalent region in New York City were consecutively recruited (180 women total) for an HIV/STD risk determinant and intervention study. The women tended to be working class, predominantly African–American and Latina (68% and 20%, respectively), single (91%), and without a history of intravenous drug use. Based on detailed close-ended and qualitative interviews, sexual risk for HIV/STD was reflected in a history of at least one STD (60%) of the women, multiple male sexual partners (1–31; median: 5), and inconsistent or no condom use in the past 3 months (75% of the women). *Results*: Women's strategies for HIV/STD protection were intertwined with contraceptive practices. Beyond sporadic or no use of male condoms, women reported that over the previous 3 months they had used spermicides (15%), the diaphragm (4%), the sponge (3%), the female condom (1%), in addition to birth control pills (52%) and Norplant (5%). Behavioral strategies to avoid the risk of HIV/STD included non-penetrative sex (outercourse) for 36%, withdrawal for 38%, deciding not to become involved in a relationship (6%), and leaving a partner (4%). The male condom ranked highest in women's effectiveness ratings for protection against HIV/STD, followed by the female condom and to a lesser extent the diaphragm and spermicides. Women stated the following reasons for not using male condoms: partner's refusal (25%), women's own reluctance (25%), interference with sexual behavior (27%), carelessness (18%), no availability of condoms (17%), and the use of other birth control methods (11%). Reasons for discontinuation of male condom use included trust in male partners or use of other methods. *Conclusion*: Male condom use for HIV/STD protection among heterosexual women and their male partners remains inconsistent. There is an urgent need to expand women's repertoire of protection by raising awareness of the effectiveness of other barrier methods and alternative sexual behavior and by rapidly developing new microbicides/virucides so that women can be in control.

III.A–40
Women's Preferences Regarding the Formulation of Over–the–Counter Vaginal Spermicides.

Form: Journal Article.
Author: Elias, C. J.[1]; Coggins, C.[1]; Atisook, R.[2]; Bassett, M. T.[3]; Ettiegne–Traore, V.[4]; Ghys, P. D.[4]†; Jenkins–Woelk, L.[3]; Thongkrajai, E.‡; VanDevanter, N. L.‡‡. [1]Population Council, NY, U.S.A.; [2]Siraraj Family Health Research Center, Bangkok, Thailand; [3]University of Zimbabwe, Harare, Zimbabwe; [4]Projet RETRO–CI, Abidjan, Cote d'Ivoire; †Institute of Tropical Medicine, Antwerp, Belgium; ‡Khon Kaen University, Khon Kaen, Thailand; ‡‡Columbia University, School of Public Health, NY, U.S.A.

Source: Th.C.322, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Issue*: There is an urgent need for safe, effective, and acceptable woman–controlled barrier methods for the prevention of sexually transmitted diseases (STDs). Very little information is known about the desirable characteristics of vaginal preparations from diverse populations of women who would potentially use such microbicidal products. Such data are essential for guiding the development of new vaginal preparations and for determining the broader application of existing spermicides. *Project*: One hundred and thirty sexually active women were enrolled among five study sites in Cote d'Ivoire, Thailand (2 sites), the United States, and Zimbabwe. Each woman used three different vaginal spermicide preparations containing nonoxynol–9—a gel, a suppository, and a film—for a period of 4 weeks per product. Pre– and post–use focus group discussions, as well as monthly, structured interviews, were used to explore the women's expectations and experiences with vaginal product use. Regular clinical exams were performed to evaluate the occurrence of irritation during "typical use" of the three preparations. *Results*: The women's specific product preferences were found to vary substantially both within and between geographic sites. Women's formulation preferences were strongly influenced by concerns about a product's lubricant (or drying) effect, its "messiness," storage requirements and disposability, and perceptions of the product's association with sexual health, frequency, and pleasure. Communication with male partners concerning vaginal product use was found to be an extremely important factor influencing women's preferences among this population of generally monogamous women. Significant side effects and evidence of vaginal irritation were uncommon findings. *Lessons Learned*: The formulation preferences of women must be considered in the development and introduction of vaginal microbicides. The specific characteristics of vaginal products and their interaction with sexual pleasure and communication will strongly determine the acceptability—and ultimately the effectiveness of use—of women–controlled methods of STD prevention.

III.A–41
The Women's Safer Sex Hierarchy: Initial Responses to Counseling on Women's Methods of STD/HIV Prevention at an STD Clinic.

Form: Journal Article.
Author: Gollub, E. L.[1]; French, P.[2]; Latka, M.[1]; Johns, L.[1]; Blum, L.[1]; O'Donnell, J.[2]; Stein, Z. A.[3] [1]Philadelphia Department of Public Health; [2]Medical College of Pennsylvania, PA, U.S.A.; [3]Columbia University, New York, NY, U.S.A.
Source: Mo.D.583, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: The goal of this article was to measure the differences in risk of reinfection with sexually transmitted diseases (STDs) and unwanted pregnancies through comparison of three different counseling messages in a clinical trial. The three messages were full choice ("hierarchy") of women's barrier methods (such as female condoms, diaphragms, and spermicides); enhanced counseling only on male condoms; and counseling only on female condoms. *Methods*: More than 1,600 attendees of STD clinics have been randomized to receive 3 different counseling messages since May 1995. Following counseling, all participants anonymously rated the intervention and answered knowledge questions based on the specific counseling received. As of January 1, 1996, there were 233 women enrolled in an intensive followup (FU) cohort for acceptability data. Two–week FU behavioral data on sexual risk were compared with intake data. In addition, choices of the 119 participants in the hierarchy FU group were tabulated and evaluated for their relationships to previous method use. *Results*: On a scale from 1 (highest) to 5 (lowest), mean responses ranged from 1.1 to 1.9 for ratings of counselors and for the ratings of video and group discussions/interactive educational approaches in the clinic. Of the women counseled on the hierarchy of women's protective options, 74% understood the nature of hierarchical risk following the counseling. Among the subset of 119 participants, the choices were as follows: the female condom (87%), the male condom (63%), spermicidal foam (61%), spermicidal film (57%), spermicidal suppository (33%), diaphragm (11%), and cervical cap (6%). (The choices were non–exclusive.) The reduction in the number of unprotected acts of intercourse after 2 weeks obtained by self–report was highest in the hierarchy arm compared with the female condom and male condom arms: 83%, 54%,

and 39%, respectively. Male condom users at intake tended to supplement condom use rather than replace it with other methods. Enrollment for the female condom was significantly easier than for the male condom. *Conclusions*: Initial results from this large, STD–clinic–based intervention suggest that a video and group discussion design was well liked. Furthermore, the hierarchical message appears to have been understood by a majority, and the methods were used for risk reduction in the 2–week FU period. When exposed to the hierarchy, male condom users tended to supplement condom use rather than substitute it with use of other methods. The female condom and other female barriers are viable risk–reduction options at an STD clinic. Long–term acceptability and effectiveness will be determined over subsequent FUs (up to 1 year).

III.A–42

Relevance and Feasibility of Clinical Trials of Topical Virucides Designed for Rectal Administration Among U.S. Gay Men.

Author: Gross, M.[1], Buchbinder, S.[2], Celum, C.[3,4], Critchlow, C.[4,5], Heagerty, P.[5]; Seage, G. R.[1] and The HIV Network for Efficacy Trials (HIVNET). [1]Abt Associates Inc., Cambridge, MA; [2]San Francisco Department of Public Health, San Francisco, CA; [3]Harborview Medical Center, Seattle, WA; [4]University of Washington, Seattle, WA; [5]Fred Hutchinson Cancer Research Center, Seattle, WA.
[See abstract II.D.iii–11.]

III.A–43

Vaginal Microbicide Use: Knowledge and Attitudes in a Cohort of Intravenous Drug Users.

Form: Journal Article.
Author: Macalino, G. E.; Celentano, D.; Hilton, C.; McFadden, C.; Vlahov, D. Johns Hopkins School of Public Health, Baltimore, Maryland, U.S.A.
Source: Th.C.4508, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: This article assessed knowledge, attitudes, and practices regarding female–controlled microbicide use. *Methods*: Three data–collection methods were used to determine microbicide issues. 1) Thirty–five participants comprising five focus groups were sampled from a larger cohort of intravenous drug users (IVDUs), regardless of their HIV status. Participants were shown several microbicides (gels, foams, films, suppositories) and were asked to identify considerations and preferences. 2) A questionnaire was developed to quantify focus group findings in the cohort. 3) Twelve Baltimore, Maryland, area stores were surveyed regarding microbicide availability. *Results*: Focus group participants were all African American, 83.9% of the participants were women, and the participants' median age was 34.4 years. Despite familiarity with condoms and intrauterine devices (IUDs), most participants had no prior knowledge of microbicides. All participants were willing to try microbicide products, but concerns such as messiness and appearance of effectiveness were expressed. An expressed benefit was more control over contraceptive decisions. Many women stated that condom use was objectionable to their male partners, who sometimes reacted violently toward condom use; however, microbicides were an agreeable alternative to condoms because their use did not require the male partner's knowledge. Preliminary data from the questionnaire provided similar information. The pharmacy survey revealed that microbicides were found near feminine hygiene products rather than near condoms, which was not consistent with focus group expectations. *Conclusions*: In this population of IVDUs, knowledge regarding microbicides is nearly absent. Microbicide products were viewed as more acceptable to women than condoms were and therefore should be carefully developed and marketed as an additional HIV–prevention strategy.

III.A–44

Safety of a Nonoxynol–9 (N–9) Vaginal Gel in Sex Workers in Kenya.

Form: Journal Article.
Author: Stevens, C. E.[1]; Martin, H. L.[1]; Richardson, B. A.[1]; Rugamba, D.[1]; Nyange, P. M.[2]*; Mandaliya, K.[3]; Achola, J. O.[2]; Kreiss, J. K.[1] [1]University of Washington; [2]University of Nairobi; [3]Coast Province General Hospital, Mombasa, Kenya; *deceased.
Source: Th.C.323, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: This article's objective was to determine if once–daily vaginal

application of a bioadhesive gel containing 52.5 mg of nonoxynol–9 (N–9) is safe for female sex workers in Mombasa, Kenya. *Methods*: HIV sero–negative female sex workers attending a research clinic in Mombasa, Kenya, were invited to participate in this randomized, double–blind, placebo–controlled, crossover trial. Subjects were randomized to receive single–use vaginal applicators containing either N–9 or a placebo and were instructed to use an applicator once daily for 2 weeks. Subjects were examined for toxicity at the end of week 1 and week 2. The exam included colposcopy using the World Health Organization criteria for the evaluation of intravaginally administered products. After a 2–week washout phase, subjects were crossed over to the other gel (N–9 or placebo). The overall frequency of epithelial disruption in study subjects was calculated, and differences in genital epithelial reaction to the N–9 gel and the placebo were examined. *Results*: Sixty women were randomized to receive N–9 and a placebo gel. Fifty–two subjects (87%) completed both periods of the trial. Overall compliance with gel application was excellent, with 98% of N–9 applicators (714 out of 728) and 97% of placebo applicators (697 out of 722) used as directed. There was no difference in the incidence of epithelial disruption (for instance, ulceration or abrasion) detected either visually or colposcopically in women using N–9 versus those using the placebo (2 events and 2 events, respectively). Other signs of epithelial toxicity that did not lead to disruption of the epithelial barrier (for example, erythema, edema, petechiae, ecchymosis, and hemorrhage) were no different between the N–9 and placebo groups. *Conclusions*: Once–daily application of an N–9 formulation containing 52.5 mg of N–9 in a bioadhesive gel was not associated with epithelial toxicity in this cohort of female sex workers. A phase III trial to evaluate the efficacy of this product in preventing HIV infection should proceed in this population.

III.A–45
Nonoxynol–9 Lubricated Latex Condoms May Increase Release of Natural Rubber Latex Protein.

Form: Journal Article.
Author: Stratton, P.[1]; Hamann, C.[2]; Beezhold, D.[3] [1]NICHD, Bethesda, MD; [2]Smart Practice, Phoenix, AZ; [3]Guthrie Institute, Sayre, PA.
Source: Th.C.433, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: Recognition of genital tract irritation to nonoxynol–9 (N–9) with use of spermicides and condoms lubricated with N–9 has raised questions about N–9's safety and its role in preventing HIV transmission. Irritation may also be due to an increased elution of natural rubber latex (NRL) proteins by N–9. *Methods*: Five brands of condoms containing lubricants with and without N–9 were evaluated. Two nonlatex brands (Tactylon™) using lubricants with and without N–9 served as controls. NRL protein content was measured using both Lowry and Latex ELISA for Antigenic Protein (LEAP) assays. Condoms and lubricants were tested in triplicate seven to ten different times. *Results*: NRL protein levels in condoms varied from brand to brand. Using the Lowry assay, a fivefold increase in protein levels was detected for brands with N–9 compared to the brand without N–9 from the same manufacturer. The LEAP assay confirmed a fourfold increase in NRL protein levels for brands with N–9 compared to those without N–9. Lowry tests on Tactylon™ (a nonprotein polymer) were positive in those with N–9 but negative in those without N–9. The LEAP assay did not detect any NRL protein in Tactylon™. *Conclusions:* Protein tests demonstrated that latex condoms lubricated with N–9 had significantly higher NRL protein levels. N–9 may cause increases in the value or false positive results of NRL protein levels in Lowry tests. N–9 may increase NRL protein extraction from latex, which may increase the risk of developing latex hypersensitivity. Further study is warranted about the interaction between lubricants and latex condoms packaged together. From a public health view, this could alter condom manufacturing processes and could modify regulatory oversight for existing latex condoms; it also underscores the need to develop new, nonlatex condoms.

III.A–46
Phase One Study of the Safety and Tolerability of Nonoxynol–9: Histological Evidence of an Inflammatory Response.

Form: Journal Article.
Author: Ward, H.; Stafford, M.; Flanagan, A.; Rosenstein, I.; Byrne, G.; Taylor–Robinson, D.; Weber, J. N.; Kitchen, V. Imperial College School of Medicine at St. Mary's, London, UK.
Source: Th.C.324, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: The purpose of this article was to determine the safety and tolerability of intravaginal nonoxynol–9 (N–9) in a gel formulation. *Methods*: A double–blind, placebo–controlled trial was conducted on female volunteers. Forty volunteers were recruited and randomized to use a standardized volume of N–9 gel or a matched placebo every night for 1 week while abstaining from sexual intercourse. Volunteers were seen on day –21, day 0, day 7, and day 14 when they were interviewed for symptoms and screened for STDs. In addition, vaginal pH and quantitative measures of lactobacilli were taken and colposcopies were performed. Vaginal biopsies were taken at day –21 and day 7 from standardized alternate positions in the lateral vaginal fornices. *Results*: Forty subjects were recruited and completed the trial. Histological signs of inflammation were found in seven members (35%) of the N–9 group and two members (10%) of the placebo group on post–intervention biopsies (odds ratio 4.8, 95% CI 0.9, 22.2). Poor correlation was found between symptomatic, colposcopic, and histological evidence of vaginal inflammation. In five subjects (all in the N–9 group), there was both colposcopic and histological evidence of inflammation. Biopsies with inflammatory changes showed patchy sub–epithelial lymphocytic infiltration. Detailed microbiological findings will be presented. *Conclusions*: This study provides histological and colposcopic evidence that intravaginal N–9 induces an inflammatory response in the vaginal mucosa. This was observed in women who abstained from sexual intercourse. The histological findings suggest a biological mechanism to underpin the observation that use of high doses of N–9 may potentiate HIV transmission. Studies are currently under way to establish whether there is a lower dose of N–9 that retains anti–HIV efficacy while avoiding the inflammatory response and to develop other virucidal agents with lower toxicity.

III.B. Behavioral Studies–Other.

III.B–1
Knowledge and Use of Contraceptives Among Undergraduates of Ahmadu.
Author: Bell, C. S.; Enahoro, F. O.
[See III.A–3.]

III.B–2
Traditional Vaginal Agents: Use and Association With HIV Infection in Malawian Women.

Form: Journal Article.
Author: Dallabetta, G. A.; Miotti, P. G.; Chiphangwi, J. D.; Liomba, G.; Canner, J. K.; Saah, A. J.
Source: AIDS. 9(3):293–297, March 1995.

Published Abstract: Objectives: To assess the prevalence of traditional vaginal agent use in Malawian women and its association with human immunodeficiency virus (HIV) infection. Methods: Consenting, antenatal women were administered a questionnaire and screened for sexually transmitted diseases (STDs), including HIV. Results: Of the 6,603 consenting women, 886 (13%) reported using intravaginal agents for tightening and 2,222 (34%) for self–treatment of vaginal discharge and itching. A higher proportion of HIV–infected than uninfected women (17% vs. 14%) reported use of intravaginal agents for treatment (odds ratio 1.29; 95% confidence interval 1.05–1.57), but no difference in proportion was found when these agents were used for tightening. In multivariate analysis, use of vaginal agent for self–treatment was independently associated with HIV seropositivity. Conclusion: The association of HIV infection with vaginal agents for self–treatment, but not for tightening, suggests that STDs may play a role in vaginal agent usage or that the agents are used differently for the two purposes. In addition to a small increased risk of HIV infection associated with vaginal agent use, these agents may interfere with condom effectiveness or acceptability of vaginal microbicides.

III.B–3
Women's Protection From HIV/STD Infection Beyond the Male Condom.
Author: Ehrhardt, A. A.; Exner, T. M.; Hoffman, S.; Loeb, I. HIV Center for Clinical and Behavioral Studies, NYS Psychiatric Institute/Columbia University, New York, NY, U.S.A.
[See abstract III.A–39.]

III.B–4
A Study of the Formulation Preferences of Existing Over-the-Counter Vaginal Preparations.

Form: Journal Article.
Author: Thongkrajai, E.[1]; Anusorntheerakul, S.[1]; Kuchaisit, C.[2]; Bunyawong, T.[3]; Voraneethakoon, Y.[2]; Thongkrajai, P.[2]; Elias, E.[4]
[1]Faculty of Nursing, KKU; [2]Faculty of Medicine, KKU; [3]STD Control Center; [4]The Population Council, NY.
Source: Th.C.4499, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objectives*: To define the characteristics of existing vaginal products that influence user preference for these formulation and to further knowledge on risk of irritation to the vagina and cervix associated with use of products containing nonoxynol-9. *Methods*: 38 married women, currently living with husbands were included in the study. The target women were examined prior to use of three different vaginal preparations containing nonoxynol-9. Each product was use for 4 weeks for the total of 12 weeks. Pre-use focus group discussions were done. Coital log recording, 2-and 4 weeks follow up, closing interview and post-use focus group discussions were carried out as means of data collection. *Results*: Films was ranked as the most preferred preparation following with gel and suppository. Advantages and disadvantages of each product were discussed. Reports of irritations included burning sensation, itching painful urination and others which had occurred in 25 cases accounting for 5.4% of the total reported coitus. *Conclusion*: Most women felt positively about Microbicides as means for STD and AIDS prevention. It was evident that more options and preparations should be provided to suit women's needs and preferences.

III.B–5
Vaginal Microbicide Use: Knowledge and

Attitudes in a Cohort of Intravenous Drug Users.
Author: Macalino, G. E.; Celentano, D.; Hilton, C.; McFadden, C.; Vlahov, D. Johns Hopkins School of Public Health, Baltimore, Maryland, U.S.A.
[See abstract III.A–43.]

IV.A. Overviews–Literature Reviews.

IV.A–1
Sexual Transmission of Human Immunodeficiency Virus: Virus Entry Into the Male and Female Genital Tract.

Form: Journal Article.
Author: Alexander, N. J.
Source: Fertility and Sterility. 54(1):1–18, July 1990.

Published Abstract: None.
Annotators' Abstract: This article reviews current knowledge about the sexual transmission of human immunodeficiency virus type 1 (HIV–1), the virus type responsible for most AIDS cases throughout the world. Spermicides have been shown to kill HIV in vitro and to decrease the incidence of infection with syphilis, gonorrhea, candida, trichomonas, herpes, and chlamydia. In vitro screening studies show that nonoxynol–9, octoxynol, benzalkonium chloride, gossypol, povidone iodine, and chlorhexidine are virucidal; and amphotericin B and dextran sulfate inhibit HIV replication. Routes of viral entry into the female reproductive tract secretions and into the male reproductive tract are also reviewed. Animal models that can be used for studies of heterosexual transmission of HIV are described. Future research considerations are presented.

IV.A–2
Report to the National Advisory Child Health and Human Development Council, June 5, 1995.

Form: Report.
Author: Anonymous.
Source: Contraceptive Development Branch, Center for Population Research, National Institutes of Child Health and Human Development, June 5, 1996.

Published Abstract: None.
Annotators' Abstract: This report summarizes the goals and current activities of the Contraceptive Development Branch, National Institutes of Child Health and Human Development. Eight grants have been funded to provide information for developing strategies to prevent HIV transmission and pregnancy. Four products will be studied several times after installation to determine the duration of effective surfactant levels. Two new products are available. In one, the product lasts for 12 or more hours and changes from a soft cream to a persistent gel upon contact with vaginal secretions. The gel acts as a nonoxynol–9 reservoir. In the other delivery approach, the product is a hard gelatin capsule (HGC) that consists of three compartments containing nonoxynol–9: a fast–releasing layer on the outer surface, intermediate–releasing granules, and slow–releasing pellets. The HGC release system provides both rapid and long–acting spermicidal action. In vitro studies confirm the three rates of release. C31G, another antiviral and spermicidal surfactant, achieves the minimum spermicidal effective dose of 0.01%. Unlike nonoxynol–9, C31G diffuses into cervical mucus and does not interact with mucin. C31G has broad–spectrum antimicrobial activity against bacteria, fungi, yeasts, and viruses, including HIV and herpes simplex virus. C31G has been formulated into a suppository with a polyethylene glycol base and has been tested for drug release characteristics, dissolution profile, and physical characteristics.

IV.A–3
The Prophylactic Properties of the Today Sponge and Other Spermicide–Containing Contraceptives.

Form: Journal Article.
Author: Berger, K. L.; Remington, K.
Source: Advances in Contraception. 3(2):125–131, June 1987.

Published Abstract: None.
Annotators' Abstract: This review summarizes in vitro studies mimicking the milieu of the Today contraceptive sponge as a prophylactic against sexually transmitted diseases (STDs). In addition, clinical studies of today's active agent— nonoxynol–9—and studies on the acquired immunodeficiency syndrome (AIDS) are outlined. In the in vitro studies, Today sponges were soaked for several hours in a saline solution at body temperature; serial dilutions of the eluate were mixed with pathogen growth media; and 5 million infectious units of test organisms were added to the mixture. Minimum inhibitory concentrations or minimum lethal concentrations were determined. The

sponge eluate effectively inhibited growth of *Gardnerella vaginalis*, *Trichomonas vaginalis*, and *Neisseria gonorrhoeae*. Some gonorrheal strains were particularly susceptible, presumably to the citrate buffers in the sponge. *Chlamydia trachomatis* and herpes simplex virus types 1 and 2 were inhibited when grown in tissue culture. The authors estimate that nonoxynol–9 concentrations as high as 83–125 mg/ml may be achieved in women who use the sponge. This concentration is much higher than the minimum inhibitory concentration.

IV.A–4
Comment: The Use of Spermicide Containing Nonoxynol–9 in the Prevention of HIV Infection.
Author: Bird, K. D.
[See abstract II.C.ii.a–2.]

IV.A–5
Family Planning, Sexually Transmitted Diseases and Contraceptive Choice: A Literature Update–Part I.

Form: Journal Article.
Author: Cates, W. Jr.; Stone, K. M.
Source: Family Planning Perspectives. 24(2):75–84, March–April 1992.

Published Abstract: Couples who use contraceptives not only protect themselves against unwanted pregnancies, but also may reduce their risk of becoming infected with a sexually transmitted disease (STD). However, no single method is highly effective in protecting simultaneously against pregnancy and infection. Thus, couples who place high priority on minimizing both risks may have to use two methods. The need for contraceptive methods that provide effective protection against both pregnancy and STDs has been intensified by the human immunodeficiency virus (HIV) epidemic. However, progress has been slowed by the lack of integration between the STD and family planning fields. The first part of this two–part article discusses the similarities and differences between the two fields, examines the impact of STDs on contraceptive use and services, and reviews the scientific literature dealing with the effects of condoms, spermicides, and barrier–and–spermicide methods on the risk of STD transmission. Part II examines what is known about the effects of oral contraceptives, the intrauterine device (IUD), tubal sterilization, and abortion on reproductive tract infections. The second part also includes a discussion of the trade–offs involved in choosing a contraceptive and presents estimates of the first year rates of unplanned pregnancy and gonorrhea infection (given an infected partner) that would occur among women using various contraceptive methods.

IV.A–6
Family Planning, Sexually Transmitted Diseases and Contraceptive Choice: A Literature Update–Part II.

Form: Journal Article.
Author: Cates, W. Jr.; Stone, K. M.
Source: Family Planning Perspectives. 24(3):122–128, May–June 1992.

Published Abstract: Couples who use contraceptives not only protect themselves against unwanted pregnancies, but also may reduce their risk of becoming infected with a sexually transmitted disease (STD). However, no single method is highly effective in protecting simultaneously against pregnancy and infection. Thus, couples who place high priority on minimizing both risks may have to use two methods. The need for contraceptive methods that provide effective protection against both pregnancy and STDs has been intensified by the human immunodeficiency virus (HIV) epidemic. However, progress has been slowed by the lack of integration between the STD and family planning fields. The first part of this two–part article discusses the similarities and differences between the two fields, examines the impact of STDs on contraceptive use and services, and reviews the scientific literature dealing with the effects of condoms, spermicides, and barrier–and–spermicide methods on the risk of STD transmission. Part II examines what is known about the effects of oral contraceptives, the intrauterine device (IUD), tubal sterilization, and abortion on reproductive tract infections. The second part also includes a discussion of the trade–offs involved in choosing a contraceptive and presents estimates of the first year rates of unplanned pregnancy and gonorrhea infection (given an infected partner) that would occur among women using various contraceptive methods.

IV.A–7
New and Existing Spermicides With Virucidal Properties.

Form: Book Chapter.
Author: Chantler, E. N.
Source: IN: Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989. Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M., eds. New York: Wiley–Liss., pp. 303–310, 1990.

Published Abstract: None.
Annotators' Abstract: The authors review properties of nonoxynol–9, benzalkonium chloride, and biguanide chlorhexidine. Vaginal microbicidal activity and interaction with cervical mucus by these agents are reviewed.

IV.A–8
Barrier Contraceptives.

Form: Journal Article.
Author: Connell, E. B.
Source: Clinical Obstetrics and Gynecology. 32(2):377–386, June 1989.

Published Abstract: None.
Annotators' Abstract: The efficacy and use of physical and chemical barrier contraceptives are reviewed in the context of the current need to prescribe two simultaneous methods for women who are at risk both for pregnancy and sexually transmitted diseases (STDs).

IV.A–9
Contraceptive Methods and the Transmission of HIV: Implications for Family Planning.

Form: Journal Article.
Author: Daly, C. C.; Helling–Giese, G. E.; Mati, J. K.; Hunter, D. J.
Source: Genitourinary Medicine. 70(2):110–117, April 1994.

Published Abstract: The authors review the evidence for association between human immunodeficiency virus (HIV) infection and individual contraceptive methods. The authors state that family planning and HIV prevention are interrelated because specific contraceptive methods may increase or decrease the risk of HIV acquisition or transmission to a woman's partner. The role of oral hormonal contraceptives, intrauterine devices (IUDs), and spermicides in the risk for HIV acquisition is not known. The role of oral contraceptives in enhancing HIV transmission is controversial, with 2 of 21 studies demonstrating a high relative risk for HIV among users of oral contraceptives. The available studies of association between contraceptive products and HIV risk are predominantly cross–sectional and are conflicting. The authors do not draw any definitive conclusions, and they call for further research, especially prospective epidemiological studies and basic biological research on mechanisms of heterosexual transmission and the effect of contraceptives on these mechanisms. Nonoxynol–9 has been shown to be effective at lower doses in reducing HIV risk; chlorhexidine has been shown to remain active in cervical mucus; betadine, menfegol, and gossypol have shown in vitro effectiveness against HIV. Contraceptive Research and Development (CONRAD) has screened 131 potentially spermicidal compounds; 26 were found to inhibit HIV, and several of those are being tested for toxicity in animals. Future studies must focus on the impact of behavioral factors on contraceptive use.

IV.A–10
Barrier Methods of Contraception, Spermicides and Sexually Transmitted Diseases: A Review.

Form: Journal Article.
Author: d'Oro L. C.; Parazzini, F.; Naldi L.; La Vecchia, C.
Source: Genitourinary Medicine. 70(6):410–417, December 1994.

Published Abstract: Objective and Methods: To understand whether barrier methods of contraception and/or spermicides lower the risk of acquiring sexually transmitted diseases (STDs), and to quantify the protection, the authors reviewed 22 published papers that examined either the impermeability of barrier methods in vitro against STD agents or the effect of spermicides, and 60 papers reporting results of epidemiological studies on the risk for STDs in users of barrier methods. Results: They found in vitro evidence that both barrier methods and spermicides were effective against most sexually transmissible agents. Doubts

remain as to the effectiveness of barrier methods and spermicides under normal conditions of use, particularly against human papilloma virus. Natural membrane condoms are not impermeable; pores in these condoms are seen by electron microscopy. Epidemiological studies show a consistent reduction in risk for use of condoms against gonococcal infection (most studies reporting relative risk (RR) estimates around 0.4–0.6) and human immunodeficiency virus (HIV) infection (RR, 0.3–0.6 in most studies). Spermicides protect women against gonorrhea and trichomoniasis; their role against other STDs is less clear, and there is some indication of an irritative effect on the vaginal mucosa that is likely to be dose–dependent. A large amount of evidence indicates that barrier methods of contraception reduce the risk of gonorrhoea and HIV transmission, but the results are, at least in quantitative terms, less consistent for other diseases. Implications for individual choices and public health approaches should relate to frequency of exposure and also to the severity of the disease.

IV.A–11
Activity of Nonoxynol–9 Against *Chlamydia trachomatis.*
Author: Ehret, J. M.; Judson, F. N.
[See abstract I.A.i–5.]

IV.A–12
The Development of Microbicides: A New Method of HIV Prevention for Women.

Form: Report.
Author: Elias, C. J.; Heise, L.
Source: Population Council, Programs Division Working Papers, No. 6, 1993.

Published Abstract: None.
Annotators' Abstract: This document contains information about the development of female–controlled microbicides for intravaginal use in preventing the heterosexual transmission of HIV and other STDs. In the view of the authors, this is now the most important prevention option to pursue. The document discusses limitations of AIDS prevention strategies, including infidelity, sexual networking as an economic strategy, and the role of nonconsensual sex. Condom promotion strategies and STD control are also discussed. In addition, improving women's ability to protect themselves (including long–term approaches to reduce women's vulnerability, changing current programs to strengthen women's positions, and developing new prevention technologies) is discussed. Various HIV prevention technologies are discussed, including female–controlled methods such as the female condom, nonoxynol–9 and other spermicides, and barrier methods. Challenges for future development of microbicides are also discussed**.**

IV.A–13
Challenges for the Development of Female–Controlled Vaginal Microbicides.
Author: Elias, C. J.; Heise, L. L.
[See abstract III.A–15.]

IV.A–14
Relationship Between Contraceptive Technology and HIV Transmission: An Overview.

Form: Book Chapter.
Author: Fathalla, M. F.
Source: IN: Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989. Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M., eds. New York: Wiley–Liss, pp. 225–237, 1990.

Published Abstract: None.
Annotators' Abstract: The author discusses the relationship between contraceptive technology and the human immunodeficiency virus (HIV). Condom use is the only method that reduces the risk of HIV transmission if one partner is seropositive. However, the use of condoms and spermicides can destroy HIV, as well as protect against sexually transmitted diseases (STDs). There is growing evidence that STDs enhance the sexual transmission of HIV. The intrauterine device (IUD) has been recognized as the one contraceptive method that should not be used by women at high risk for STDs, including HIV infection, because of endometrial trauma. The use of "effective" contraception to prevent pregnancy in a sexually active and HIV–positive woman is the only way to control perinatal transmission. IUD insertions, tubal occlusions, and vasectomies are invasive procedures that should only be

performed when sound clinical practices for disinfection and sterilization are ensured.

IV.A–15
Condoms, Spermicides, and the Transmission of Human Immunodeficiency Virus: A Review of the Literature.

Form: Journal Article.
Author: Feldblum, P. J.; Fortney, J. A.
Source: American Journal of Public Health. 78(1):52–54, January 1988.

Published Abstract: None.
Annotators' Abstract: The effectiveness of condoms and spermicides in preventing the transmission of human immunodeficiency virus (HIV) is reviewed. In vitro spermicide studies have shown the effectiveness of nonoxynol–9 against HIV and STDs. In vivo evidence is less conclusive. Methodologic issues have hampered the interpretation of data on this issue. Research should focus on the risk of seroconversion among fully compliant condom or spermicide users (relative to nonusers per unit of time or per sexual encounter) and the efficacy of condoms or spermicides in preventing HIV transmission during vaginal, anal, and oral intercourse. In addition, the acceptability of these methods and the regularity and correctness of their use by populations and communities with different seroprevalence rates is of special concern. The authors discuss research designs that could measure method efficacy.

IV.A–16
Contraceptive Technology.

Form: Book.
Author: Hatcher, R. A.; Trussell, J.; Stewart, F. H.; Stewart, G. K.; Koval, D.; Cates, W.; Oilicar, M. S.
Source: Irvington Publishers, Inc., 522 E, 82nd Street, Suite 1, New York, NY 10028. 1994.

Published Abstract: None.
Annotators' Abstract: This book and its related teaching aids provide comprehensive contraceptive and reproductive health information. Chapters cover contraceptive technologies; STDs, including HIV; and reproductive and sexual behaviors for adolescent and adult women. International editions are available.

IV.A–17
Contraceptives and HIV.

Form: Journal Article.
Author: Howe, J. E.; Minkoff, H. L.; Duerr, A. C.
Source: AIDS. 8(7):861–871, July 1994.

Published Abstract: None.
Annotators' Abstract: This article summarizes current knowledge about the relationship between contraception and human immunodeficiency virus (HIV) infection, focusing on contraceptives as modifiers of the risk for virus acquisition, as well as the methods most suitable for HIV–infected women.

IV.A–18
Effectiveness of Condoms for Prevention of HIV Infections.

Form: Journal Article.
Author: Judson, F. N.
Source: AIDS Updates. 2(6):1–8, 1989.

Published Abstract: The potential and actual effectiveness of condoms in the prevention of human immunodeficiency virus (HIV) infections is discussed. New information, quality control efforts by manufacturers and the Food and Drug Administration, laboratory methods for testing condom permeability, and the HIV and virucidal activity of the spermicide nonoxynol–9 are emphasized. In addition, the author focuses on clinical and epidemiological studies of the use of condoms to prevent HIV infections, sales trends, user rates, and slippage and breakage rates, and on recommendations on the proper usage of condoms for vaginal and anal intercourse. When used properly, latex condoms should provide an effective physical barrier against HIV transmission. However, even under ideal use conditions, vaginal intercourse with condoms should be viewed as "very safe," rather than "completely safe." Laboratory studies indicate that concomitant use of spermicides containing nonoxynol–9 as a backup chemical barrier may further improve condom efficacy. However, nonoxynol–9 may have adverse effects on normal mucous membranes. Studies have indicated that the use effectiveness of condoms in preventing HIV infections is low, and this is due in small part to improper use, slippage, and

breakage, and, in large part, to failure to use them at all. The author suggests that effort is needed to improve condom use through enhanced availability and sense of value.

IV.A–19
Contraception and the Prevention of Sexually Transmitted Diseases.

Form: Journal Article.
Author: Kirkman, R.; Chantler, E.
Source: British Medical Bulletin. 49(1):171–181, January 1993.

Published Abstract: Sexually transmitted diseases (STDs) are a major cause of ill health in women, their sexual partners, and their children. Contraceptive methods alter in various ways the risk of acquiring an STD, but assessment of the odds ratio is difficult because of the many confounding factors. Spermicides have been reported to kill a wide range of bacteria and viruses, including human immunodeficiency virus (HIV) in vitro, and to protect in vivo from infection by gonorrhea, chlamydia, and pelvic inflammatory disease (organisms unspecified). Spermicides will not cure preexisting infections. Condoms and diaphragms will give some protection from bacterial and viral infections in all parts of the genital tract. Hormonal contraception and tubal ligation give protection to the upper genital tract but not the cervix. Carcinoma of the cervix follows the same pattern as STDs.

IV.A–20
Adolescent Contraception: Nonhormonal Methods.

Form: Journal Article.
Author: Kulig, J. W.
Source: Pediatric Clinics of North America. 36(3):717–730, June 1989.

Published Abstract: A comparison of the advantages, disadvantages, and costs of each method is presented in Table 1. Barrier methods of contraception offer adolescents protection against both pregnancy and STDs, but innovative approaches are needed to enhance availability and acceptability. Condom use in conjunction with a vaginal spermicide would provide optimal protection. The “female condom” may prove to be an effective alternative. Diaphragms and cervical caps can be prescribed for well-educated, highly motivated adolescents comfortable with insertion and removal. The vaginal contraceptive sponge provides many of the advantages of the diaphragm and cap without the need for an examination and fitting; it also may be used as a backup method with the condom. Vaginal spermicides used alone are significantly less effective than in combination with a mechanical barrier. The IUD is not considered appropriate for most adolescents due to its association with an increased risk of pelvic infection. Periodic abstinence requires accurate identification of the fertile period, extensive education, and partner cooperation. Sterilization is rarely considered an option in adolescents. Alternate forms of sexual expression are available to adolescents who choose to abstain from intercourse.

IV.A–21
Barrier Contraceptives and the Interaction Between HIV and Other Sexually Transmitted Diseases.

Form: Book Chapter.
Author: Lamptey, P.
Source: IN: Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989. Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M., eds. New York: Wiley–Liss, pp. 255–265, 1990.

Published Abstract: None.
Annotators’ Abstract: The authors review data on the effectiveness of condom and spermicide use in preventing human immunodeficiency virus (HIV) infection and other sexually transmitted diseases (STDs) as well as data on the interaction between HIV infection and other STDs.

IV.A–22
Update on Topical Microbicides.
Author: National Institute of Allergy and Infectious Disease, National Institutes of Health.
[See abstract IV.C–4.]

IV.A–23
Effectiveness of Vaginal Contraception in

Prevention of Sexually Transmitted Diseases.

Form: Book Chapter.
Author: North, B. B.
Source: IN: Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989. Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M., eds. New York: Wiley–Liss, pp. 273–290, 1990.

Published Abstract: None.
Annotators' Abstract: Vaginal spermicides (foam, jelly, cream, suppositories, the vaginal sponge) and barrier methods (diaphragm, cervical cap) may offer some protection against sexually transmitted diseases (STDs). The most widely used spermicide is nonoxynol–9. Its surfactant properties immobilize bacteria, viral pathogens, and sperm by disrupting viral envelopes and cell membranes. Nonoxynol–9 may act as an antimicrobial agent against chlamydia. The prevention of viral pathogens, such as the human immunodeficiency virus (HIV), may depend on the spermicide's dispersal on all genital surfaces in conjunction with the protection of cervical tissues and the upper genital tract. Many in vitro studies have shown that nonoxynol–9 can inhibit the growth of *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Candida albicans*, and *Treponema pallidum*. Extensive testing of the vaginal sponge has demonstrated that it is active against *N. gonorrhoeae* and herpes simplex virus type 2. Nonoxynol–9 has some effectiveness in reducing STD transmission, as many retrospective studies have illustrated.

IV.A–24
Vaginal Contraceptives: Effective Protection From Sexually Transmitted Diseases for Women?

Form: Journal Article.
Author: North, B. B.
Source: Journal of Reproductive Medicine. 33(3):307–311, March 1988.

Published Abstract: The use of vaginal contraceptives reduces the risk of a woman's contracting sexually transmitted diseases (STDs). Almost 2 decades of laboratory data have established the virucidal and bactericidal characteristics of the spermicide nonoxynol-9; clinical trials, albeit limited, have confirmed its effectiveness. The use of spermicides in conjunction with mechanical barriers, such as the condom, diaphragm, contraceptive sponge, and cervical cap, may provide optimal STD prophylaxis. Such information should be conveyed to women who are at risk of contracting or transmitting STDs.

IV.A–25
The Vagina as an Ecologic System. Current Understanding and Clinical Applications.

Form: Journal Article.
Author: Overman, B. A.
Source: Journal of Nurse–Midwifery. 38(3):146–151, May–June 1993.

Published Abstract: Recent advances in understanding the mechanisms by which *Lactobacillus acidophilus* dominates the healthful microecology of the vagina through microbicidal enzyme systems has led to renewed interest in ecological approaches to vaginal health maintenance and to the treatment of vaginosis and vaginitis. Review of pertinent research suggests that because of inadequate adherence of lactobacilli from dairy sources, contaminants in commercial sources, and the failure of sparse clinical trials to show evidence of effectiveness, intravaginal applications of *L. acidophilus* cannot be recommended. Bacterial vaginosis is described in this article as a microecological shift in the dominant organism of the microecology from *L. acidophilus* to *Gardnerella vaginalis*. This results in conditions favorable to vaginal establishment of many anaerobic organisms. The ability to identify and nurture healthful lactobacilli in the vaginal microflora is suggested as a future direction for health–oriented research, practice, and screening.

IV.A–26
Efficacy of Barrier Methods in Contraception. (Advances in Gynecology and Obstetrics. Series Vol. 1.)

Form: Book Chapter.
Author: Potts, M.; McIntyre, S.
Source: IN: Fertility, Sterility, and Contraception. Belfort, P.; Pinotti, J. A.; and Eskes, T. K., A. B., eds. Carnforth, England:

Parthenon Publishing Group. 1989, pp. 279–285.

Published Abstract: None.
Annotators' Abstract: With the recent spread of sexually transmitted diseases (STDs) and acquired immunodeficiency syndrome (AIDS), there is an increased need for effective contraceptives that prevent such diseases. This chapter reviews the history of barrier contraceptives and the methods used to evaluate their effectiveness against primary and STDs.

IV.A–27
[Contraception and Sexually Transmitted Disease.] [French.]

Form: Journal Article.
Author: Serfaty, D.
Source: Contraception, Fertilite, Sexualite. 16(11):927–934, 1988.

Authors' Abstract: Some contraceptive methods promote or aggravate sexually transmitted diseases (STDs); others have the opposite effect, protecting against STDs. Approximately 2% of women using inert or copper intrauterine devices (IUDs) run the risk of pelvic infection during the first year of use. Among users of the IUD, the following women are in the high–risk group for pelvic infection: nulliparas, women under 25 years of age, users of the Dalkon Shield, women likely to contract STDs, immunodepressed women, and pregnant women using IUDs. It appears that the risk of pelvic infection associated with IUD use is more lifestyle– and sexuality–related than it is user–related. Genital mycoses are more frequent at the endocervical level in users of oral contraceptives and vaginal contraceptive sponges containing nonoxynol–9. *Chlamydia trachomatis* appears to be more common at the endocervical level in women who use the pill than in those who do not. Vaginal contraception (condom, diaphragm, and spermicides) protects against many STDs, pelvic infection, and tubal sterility. In conclusion, the anti–STD effect and, in particular, the anti–acquired immunodeficiency syndrome (AIDS) effect of various barrier contraceptive methods (in vivo as well as in vitro) are discussed in detail in this article.

IV.A–28
Studies on the Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease and Other Genital Infections and Contraception. II. Effect In Vitro of Vaginal Contraceptive and Non–Contraceptive Preparations on *Treponema pallidum* and *Neisseria gonorrhoeae*.

Form: Journal Article.
Author: Singh, B.; Cutler, J. C.; Utidjian, H. M.
Source: British Journal of Venereal Diseases. 48(1):57–64, February 1972.

Published Abstract: None.
Annotators' Abstract: In vitro studies were conducted to identify a product that simultaneously prevents conception and genital infection. Twenty vaginal contraceptive preparations and 17 other compounds, mostly vaginal antiseptics, were studied in vitro for their effect on the motility of *Treponema pallidum* and for their bactericidal or bacteriostatic effects on *Neisseria gonorrhoeae*, the two most frequently occurring venereal disease organisms. The in vitro tests used for the study were adopted from the *U.S. Food and Drug Administration Methods for Testing Antiseptics and Disinfectants* (1931). The spirocheticidal effect on *T. pallidum* was studied according to the methods of Arnold and Cutler and Turner, Hollander, and Schaeffer, which measure the time required to immobilize spirochetes. Two methods—time exposure and plate dilution—were used for determining the bactericidal and bacteriostatic effect on *N. gonorrhoeae*. All in vitro results are reported. Two contraceptives and three noncontraceptives immobilized *T. pallidum* spirochetes within 1.0 to 1.5 minutes at the lowest concentration of 1%. In most instances, the contraceptive dilution that was effective by the time–exposure technique was also effective by the plate–dilution method. Two preparations inhibited bacterial growth after 1 minute of exposure, and two preparations were effective, according to the plate–dilution method, at a concentration of 1%. The authors conclude that further studies are required to find the preparations that show the greatest potential for topical use in venereal disease prophylaxis and contraception.

IV.A–29
Avoiding Sexually Transmitted Diseases.

Form: Journal Article.
Author: Stone, K. M.
Source: Obstetrics and Gynecology Clinics of North America. 17(4):789–799, December, 1990.

Published Abstract: None.
Annotators' Abstract: As the spectrum of sexually transmitted diseases (STDs) has broadened to include many infections that are not readily cured, the prevention of STDs has become more important than ever. Primary prevention methods include abstinence, careful selection of sexual partners, condoms, vaginal spermicides, and a vaccine for hepatitis B virus. Condoms will protect against STDs only if used consistently and correctly; vaginal spermicides may also reduce the risk of certain STDs. Health care providers should routinely counsel women on methods to reduce the risk of STDs.

IV.A–30
Vaginal Microbicides for Preventing the Sexual Transmission of HIV.
Author: Stone, A.; Hitchcock, P. J.
[See abstract III.A–34.]

IV.A–31
Spermicides, HIV, and the Vaginal Sponge.

Form: Journal Article.
Author: Stone, K. M.; Peterson, H. B.
Source: JAMA. 268(4):521–523, July 22–29, 1992.

Published Abstract: None.
Annotators' Abstract: The authors review several difficulties in methodology for conducting research on vaginal microbicide effectiveness. They note that expectations about efficacy in preventing sexually transmitted disease (STD) are often inferred from contraceptive efficacy. However, since the prevention of pregnancy is biologically and psychologically much different, data on the effectiveness of spermicides in preventing pregnancy cannot be extrapolated to their use in preventing STDs.

IV.A–32
Prevention of Sexually Transmitted Infections: Physical and Chemical Barrier Methods.

Form: Book Chapter.
Author: Stratton, P.; Alexander, N. J.
Source: Infectious Disease Clinics of North America. 7(4):841–859, December 1993.

Published Abstract: Barrier contraceptives, including mechanical methods, chemical methods, and combinations thereof, have the potential to decrease the spread of STDs, are inexpensive, and do not have any systemic effects. Currently, the concerns that the efficacy of latex condoms is limited because they are not consistently used, they can break, may cause allergies, and have a limited shelf–life has led to the development of condoms made of other materials such as polyurethane. Spermicides using nonoxynol–9 as their active ingredient have been shown to be effective in preventing the transmission of some STDs such as gonorrhea and chlamydia. In the absence of well–controlled studies of nonoxynol–9 efficacy against HIV, questions have been raised that some formulations, high doses, or frequent use may be associated with genital tract irritation, and possible enhancement of HIV transmission. Because heterosexual transmission will continue to be the major route of HIV transmission worldwide, the development and consistent use of a chemical or mechanical barrier during intercourse may be the best way to decrease the spread of HIV.

IV.A–33
Barrier Contraception: A Comprehensive Overview. [Review.]

Form: Journal Article.
Author: Tatum, H. J.; Connell-Tatum E. B.
Source: Fertility & Sterility. 36(1):1–12, July 1981.

Published Abstract: The barrier class of contraceptives, used either alone or with supplementary spermicidal agents, includes the most ancient of methods for the control of human fertility. Modern innovations have effected marked improvement in their efficacy and acceptability, so that they have become the key means of controlling fertility in the world today. The traditional diaphragms and condoms decreased in popularity to some extent when methods such as oral contraceptives and intrauterine devices became available for general use. However, the plain or medicated barriers are regaining their rightful position in

our contraceptive armamentarium as more and more questions are being raised about the real or potential adverse side effects of systemic and intrauterine contraceptives. There is evidence throughout the world of the growing popularity and use of locally acting mechanical and/or spermicidal contraceptive methods. Their impact upon the increasing world population can be expected to become even greater when the true need for the control of fertility becomes more generally recognized and appreciated.

IV.A–34
Scientists Zero In on New HIV Microbicides.

Form: Journal Article, News.
Author: Voelker, R.
Source: JAMA. 273(13):979–980, April 5, 1995.

Published Abstract: None.
Annotators' Abstract: This report summarizes a meeting on microbicides. Various mechanisms of action, such as blocking HIV–infected lymphocytes from attaching to cervical epithelium, and novel delivery systems, including temperature–sensitive gels, were discussed. Properties of carrageenan candidate microbicides were discussed; iota–carrageenans completely blocked the attachment of HIV–infected lymphocytes to epithelial cells after 90 minutes of incubation.

IV.A–35
[Real and False Risk of Local Contraception: Spermicides and the Diaphragm.] [French.]

Form: Journal Article.
Author: Zufferey, M. M.
Source: Journal de Gynecologie, Obstetrique et Biologie de la Reproduction. 14(3):359–363, 1985.

Published Abstract: A critical analysis of recent publications about spermicides and the side effects of them is made in this article. The modern spermicides consist principally of nonoxynol–9 and benzalkonium chloride. The products are harmless and efficient when used correctly for every act of sexual intercourse. In vivo testing with rabbits and rats shows that nonoxynol–9 is absorbed through the vaginal wall. Benzalkonium chloride is not absorbed, as shown by in vivo tests in rats and women. The diaphragm as a method of contraception has some drawbacks, but they seem harmless (allergy to rubber or septic shock syndrome are very rare).

IV.A–36
Methodologic Issues in Microbicidal Development

Form: Journal Article
Author: Scarlett, M.; Duerr, A. Centers for Disease Control and Prevention Atlanta, GA.
Source: Th.C.4505, XI International Conference on AIDS, July 1996, Vancouver, BC, Canada.

Authors' Abstract: *Objective*: To review existing literature associated with use of intravaginal agents to prevent sexual transmission of HIV/STD(microbicides). *Methods*: Searches of peer-reviewed journals in public health, medical, and social sciences literature. Searches included Medline,Current Contents, (1976-1995) and reference tracing included in results. *Results*: A total of 220 sources (journal articles, book chapters, published reports and policy statements), 103 on effectiveness and adverse effects, were reviewed. The most thoroughly investigated microbicide is nonoxynol-9 (N-9); a clinical trial demonstrated protection against gonorrhoea and trichomoniasis. N-9 was shown to be effective against HIV in vitro in 1985; the effectiveness of N-9 against HIV in vivo has been inconsistent in several clinical studies. Studies of other agents, such as chlorhexidine, gramicidin, and octoxynol, have also demonstrated in vitro effectiveness against HIV. The frequency with which adverse reactions occur with microbicide use is unclear for several reasons including: 1) appropriate control and/or placebo groups were not included; 2) no standard method for determination of frequency of adverse reactions was used (some used colposcopy, whereas others used visible observation of genital lesions, with no colposcopy); 3) varying study protocols, making it difficult to determine whether adverse effects could be attributed to high dosages, specific formulations, or frequency of use; and 4) the impact of "inert" ingredients (e.g.methylcellulose, parabens, alcohol, perfumes) added to formulations of microbicides is not known. *Conclusion*: Because of differences in study design, comparison of effectiveness and adverse reactions associated with different spermicidal/microbicidal agents is not currently feasible. The role of additional

labeled ingredients in producing adverse effects, including teratogeneity, is not precisely known. Future studies towards the development of microbicides would benefit from use of a standard formulation and three groups in clinical trials: a trial group, a comparable placebo, and a control group using no intravaginal agent to assure proper interpretation and comparability of results.

IV.B. Overviews–Commentary/Recommendations.

IV.B–1
Counseling to Prevent HIV Infection and Other Sexually Transmitted Diseases. The U.S. Preventive Services Task Force.

Form: Journal Article.
Author: Anonymous.
Source: American Family Physician. 41(4):1179–87, April 1990.

Published Abstract: The U.S. Preventive Services Task Force recommendations on human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs) are reviewed and discussed. The Task Force recommends that clinicians take a complete sexual and drug use history of all adolescent and adult patients. Sexually active patients should be advised that abstaining from sex or maintaining a mutually faithful sexual relationship with a partner who is known to be uninfected are the most effective strategies to prevent infection with HIV or other STDs. Patients should also receive counseling about the indications and proper methods for using condoms and spermicides in sexual intercourse and about the health risks associated with anal intercourse. Intravenous drug users should be encouraged to enroll in a drug treatment program and should be warned against sharing drug equipment or using unsterilized needles and syringes. All patients should be offered testing in accordance with recommendations on screening for syphilis, gonorrhea, chlamydial infection, genital herpes, hepatitis B, and HIV infection.

IV.B–2
Counseling Women With HIV Infection About Pregnancy, Heterosexual Transmission and Contraception.

Form: Journal Article.
Author: Bury, J. K.
Source: British Journal of Family Planning. 14(4):116–122, January 1989.

Published Abstract: Recent evidence suggests that pregnancy might not be dangerous for women who are infected with the human immunodeficiency virus (HIV) as long as they remain well. The risk of transmission to the baby may also not be as great as was once thought. Women with HIV infection may infect their sexual partners during vaginal intercourse. It is recommended that they avoid intercourse if they can; if not, however, they may need a method of contraception to prevent pregnancy, as well as a barrier method to prevent heterosexual transmission. The author states that these methods must not increase the risk of progression to acquired immunodeficiency syndrome (AIDS). Also, it is suggested that a woman with HIV infection who remains well may continue with her usual method of contraception, and ideally should use a condom and spermicide as well. If she has an intrauterine device (IUD), however, she should be advised to have it removed.

IV.B–3
Commentary: The Quest for Women's Prophylactic Methods—Hopes vs. Science.

Form: Journal Article.
Author: Cates, W. Jr.; Stewart, F. H.; Trussell, J.
Source: American Journal of Public Health. 82(11):1479–82, November 1992.

Published Abstract: The companion article by Rosenberg and Gollub in this issue summarizes data from 10 observational studies and concludes that female–controlled contraceptive methods, under typical conditions, are comparable to condoms in preventing sexually transmitted diseases (STDs), and should be merchandized as such. While we agree that chemical and mechanical contraceptives provide protection against some STDs, we think the authors have overstated the case for these methods, especially in comparison with the condom. We think the current data remain inconclusive regarding the absolute protection of spermicides against human immunodeficiency virus and their level of protection—relative to that of the condom—against other STDs. Three reasons account for our differences: the limitations in the comparative data; the reported adverse effects of spermicides on vaginal conditions, including vaginal ulcers; and the relative value of condoms, even under typical conditions, in preventing STDs. For these reasons, we would currently counsel both men and women who

practice high–risk sexual behaviors to use condoms as their first line of defense. If this is unacceptable, the female barriers become a fallback position to protect against bacterial STDs.

IV.B–4
Challenges for the Development of Female–Controlled Vaginal Microbicides.
Author: Elias, C. J.; Heise, L. L.
[See abstract III.A–15.]

IV.B–5
Nonoxynol–9: The Need for Policy in the Face of Uncertainty.

Form: Journal Article, Editorial.
Author: Elias, C. ; Heise, L. L.
Source: AIDS. 9 (3): 311–312, 1995.

Published Abstract: None.
Annotators' Abstract: The authors respond to Wittkowski's editorial (see IV.B–26). The authors agree that there is an urgent need to determine the potential role of nonoxynol–9 (N–9) in augmenting women's HIV prevention options and a need for more public policies. They disagree with Wittkowski's assertion that the safety and efficacy of N–9 have been demonstrated beyond a reasonable doubt. The authors point out that the limitations in the design and implementation of studies of N–9 are sufficient to call for new well–designed and controlled clinical trials. Moreover, the authors state that women should be informed about current understanding of the relative benefits and risks of using vaginal spermicides for HIV prevention under various conditions of use, as incomplete and inconclusive as it is. Policy makers should encourage public discussion of the relative risks and benefits that these data reveal. Such discussions should include women at risk for HIV infection. Social scientists should be included in research on microbicides. The authors raise the question of how to design hierarchial messages that convey the complexity of using various HIV prevention methods.

IV.B–6
Condoms, Spermicides, and the Transmission of Human Immunodeficiency Virus: A Review of the Literature.

Author: Feldblum, P. J.; Fortney, J. A.
[See abstract IV.A–15.]

IV.B–7
Nonoxynol–9 and the Reduction of HIV Transmission in Women.

Form: Journal Article.
Author: Gollub, E. L.; Stein, Z.
Source: AIDS. 6(6):599–601, June 1992.

Published Abstract: None.
Annotators' Abstract: The authors respond to findings and opinions in Bird's review of the literature on nonoxynol–9. They cite the lack of significant findings about the toxicity of nonoxynol–9, and they discount the use of six references that do not refer to safety. The authors also state that study by Kreiss et al. on use of the sponge by commercial sex workers in Kenya noted toxicity at a nonoxynol–9 dosage of 1,000 mg instead of the usual 60–360 mg. In addition, Rekart's reports of adverse effects of nonoxynol–9 in a survey of commercial sex workers included women's perception of irritation, but medical examinations had not been performed. Moreover, no control group using non–nonoxynol–9 lubricated condoms was used. Niruthisard et al. reported that the studies of the effects of frequent nonoxynol–9 use on the vagina and cervical mucosa focused on women who were not sexually active. Thus, the dilution factors of semen and vaginal secretions could not be observed. Although the authors disagree with Bird's studies documenting irritation without clinical outcomes, they agree with Bird that many questions remain unanswered and require continued research.

IV.B–8
HIV, Heterosexual Transmission, and Women.

Form: Journal Article.
Author: Guinan, M. E.
Source: JAMA. 268(4):520–521, July 22–29, 1992.

Published Abstract: None.
Annotators' Abstract: This article outlines the need for female–controlled methods of protection against infection with human immunodeficiency virus (HIV). Lessons learned from family planning programs show that

contraception methods that are used by women and that do not depend on partner consent (e.g. oral contraceptives) are the most effective for protecting against pregnancy.
Female–controlled contraceptives that may provide some protection against sexually transmitted diseases (STDs) and sexually transmitted HIV include spermicides (such as nonoxynol–9 in a variety of formulations) and barriers (such as the diaphragm and cervical cap). Whether nonoxynol–9 formulated in a barrier other than a sponge would be any more effective against the transmission of HIV to women remains unknown. The author concludes that the diaphragm and the cervical cap are unlikely to protect against HIV because the virus may infect through the vagina; protection against HIV infection by the female condom has not been established.

IV.B–9
Recommendations for the Development of Vaginal Microbicides.
Author: The International Working Group on Vaginal Microbicides.
[See abstract III.A–20.]

IV.B–10
Effectiveness of Condoms for Prevention of HIV Infections.
Author: Judson, F. N.
[See abstract IV.A–18.]

IV.B–11
Boost for Vaginal Microbicides Against HIV.

Form: Journal Article.
Author: Lange, J. M.; Karam, M.; Piot, P.
Source: Lancet. 342(8883):1356, November 27, 1993.

Published Abstract: None.
Annotators' Abstract: A meeting on vaginal microbicides was convened by the World Health Organization (WHO). Although ideally products would prevent the transmission of sexually transmitted diseases (STDs), compounds that act more selectively, that is, against the human immunodeficiency virus, should still be developed. Animal models to evaluate potential compounds should not be viewed as replacements for safety and efficacy studies in humans. WHO, in collaboration with others, should devise prototype protocols for the clinical evaluation of vaginal microbicides and the development of surrogate efficacy endpoints for phase II trials.

IV.B–12
Health Effects of Contraception.

Form: Book Chapter.
Author: Lee, N. C.; Peterson, H. B.; Chu, S. Y.
Source: IN: Contraceptive Use and Controlled Fertility Health Issues for Women and Children. Background papers. Parnell, A. M., ed. Washington, D.C.: National Academy Press., pp. 48–95, 1989.

Published Abstract: None.
Annotators' Abstract: The authors present a detailed account of the health effects of various widely available and highly effective methods of contraception. Oral contraceptives have been proven highly effective in preventing pregnancy, reducing the risk for endometrial and ovarian cancers and pelvic inflammatory disease, decreasing the risk for benign breast disease, and decreasing the concentration of high–density lipoprotein cholesterol. On the negative side, oral contraceptives increase the risk for cardiovascular disease, especially venous thromboembolism, and the risk for hepatocellular adenoma. Intrauterine devices (IUDs) are highly effective: method failure rates are approximately 1% per year for medicated IUDs and 2% per year for nonmedicated IUDs. No major noncontraceptive health benefits are linked with IUD use. Four major health risks are associated with IUD use: spontaneous abortion, which rarely may progress to septic abortion; uterine perforation; pelvic inflammatory disease; and tubal infertility. Because of the potential for preventing the transmission of sexually transmitted diseases (STDs) such as human immunodeficiency virus (HIV) infection, researchers are focusing on barrier methods of contraception. The estimated method failure rate for condom use is 2% per year, while the user failure rate is 12%. The method failure rate for spermicides is estimated to be about 3% per year; however, the user failure rate is much higher, at 21% per year. The method failure rate for use of diaphragm with spermicide is estimated to be about 3% per year, but the user failure rate is much higher, at 18% a year.

IV.B–13

Whatever Happened to the Contraceptive Revolution?

Form: Journal Article.
Author: Lincoln, R.; Kaeser, L.
Source: Family Planning Perspectives. 20(1):20–24, January–February 1988.

Published Abstract: None.
Annotators' Abstract: This article reviews experience with contraceptive methods since the modern era of contraception began in the 1950s. The widespread concern about the AIDS epidemic represents both an opportunity and a challenge to those involved in contraceptive development. Priorities in contraceptive research need to be reexamined to include methods that can simultaneously address both unintended pregnancy and AIDS, as well as less lethal sexually transmitted diseases. None of the new methods currently receiving research and development attention meet these criteria. However, with adequate funding and the removal of development barriers, promising leads for new birth control methods could become realities. Finally, the authors suggest increasing contraceptive education for the general public, health professionals, legislators, and consumer and women's groups.

IV.B–14
Vaginal Contraceptives: Effective Protection From Sexually Transmitted Diseases for Women?
Author: North, B. B.
[See abstract IV.A–24.]

IV.B–15
Development of Vaginal Microbicides for the Prevention of Heterosexual Transmission of HIV.

Form: Journal Article.
Author: Pauwels, R.; De Clercq, E.
Source: Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology. 11(3):211–221, March 1, 1996.

Published Abstract: Various compounds could be considered to be vaginal microbicides, preventing heterosexual transmission of HIV (i.e., virucidal agents such as nonoxynol–9 and chlorhexidine) and antiviral agents interfering with either virus adsorption/fusion (polyanionic substances such as polysulfates (i.e., PVAS, PAVAS), polysulfonates, polycarboxylates, polyoxometalates, and negatively charged albumins), or fusion or uncoating agents (bicyclams); or reverse transcription agents (dideoxynucleoside analogues, acyclic nucleoside phosphonates (i.e., PMEA, PMPA), non-nucleoside reverse transcriptase inhibitors (i.e., TIBO, HEPT), and alpha-APA derivatives). In particular, combinations of two or more of these compounds seem to be an attractive approach to interrupt transmission of HIV at different stages of the infectious process.

IV.B–16
The Urgent Need for a Vaginal Microbicide in the Prevention of HIV Transmission.

Form: Editorial.
Author: Potts, M.
Source: American Journal of Public Health. 84(6):890–891, June 1994.

Published Abstract: None.
Annotators' Abstract: The author argues that the development of vaginal microbicides is imperative in preventing or impeding the heterosexual transmission of human immunodeficiency virus (HIV). Although condoms, consistently and correctly used, are highly effective in preventing HIV, the use of a microbicide may be helpful in situations in which women cannot ensure consistent or correct condom use. In vitro activity against HIV has been demonstrated with nonoxynol–9, chlorhexidine, benzalkonium chloride, gossypol, and dextran sulfate, and their use is approved in humans. The author calls for a coordinated program of international research to conduct studies on more than one product and formulation, as well as an accelerated review process by the Food and Drug Administration (FDA) to allow the labeling of a vaginal microbicide as protection against HIV. The author also discusses ethical and study design issues relevant to clinical trials of microbicides.

IV.B–17
[How Can a Female Protect Herself From HIV Infection?] [German.]

Form: Journal Article.
Author: Raab, V. W.
Source: Fortschritte der Medizin.

107(27):572–575, September 20, 1989.

Published Abstract: In view of the changing patterns within population groups affected with acquired immunodeficiency syndrome (AIDS), the need for preventing transmission of the disease during heterosexual genital intercourse is becoming increasingly important. How the woman can protect herself without the help of her partner has so far received little attention. When condoms are not used, a woman can be infected by human immunodeficiency virus (HIV) during genital intercourse. The use of vaginal foam tablets containing 75 mg of nonoxynol–9, which have been used for contraception for many years, seems to be a valuable method of protection. The virucidal threshold concentration for nonoxynol–9, established in numerous in vitro studies, is far exceeded in practical intravaginal use of the foam tablets. The author suggests that additional protection for the woman may be afforded by the use of a vaginal diaphragm.

IV.B–18
Commentary: Methods Women Can Use That May Prevent Sexually Transmitted Disease, Including HIV.

Form: Journal Article.
Author: Rosenberg, M. J.; Gollub, E. L.
Source: American Journal of Public Health. 82(11):1473–78, November 1992.

Published Abstract: Although sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV), are a major concern for women, few prevention messages are targeted specifically to women. Messages that are targeted to women stress the following advice: abstaining, altering the number or selection of partners, and urging partners to use condoms. These behaviors may be unrealistic for many women, particularly women who are at the highest risk for STDs, because they require significant changes in lifestyle or depend on male–controlled condom use. Recommendation of contraceptives for prevention of STDs depends largely on how well specific methods perform under controlled conditions, either in the laboratory or in clinical trials. Observational studies, which better reflect day–to–day use, indicate that condoms, barriers, and spermicides, used properly and consistently, can provide substantial protection against various STDs. Condoms can similarly help protect against HIV, but studies of barriers and spermicides are scant and currently inconclusive. Finally, those methods that are controlled by women are consistently more effective in preventing STDs. Thus, although condoms used well are still the best choice, the imperative for female–controlled methods indicates that diaphragms and spermicides should receive greater emphasis in prevention messages.

IV.B–19
Virucides in Prevention of HIV Infection. Research Priorities. World Health Organization Working Group on Virucides.
Author: Rosenberg, M. J.; Holmes, K. K.
[See abstract III.A–26.]

IV.B–20
Priorities for Vaginal Microbicide Research.

Form: Journal Article, Letter.
Author: Sokal, D. C.; Hermonat, P. L.
Source: American Journal of Public Health. 85(5):737–738, May 1995.

Published Abstract: None.
Annotators' Abstract: The authors propose that determining the effectiveness of a vaginal microbicide against human papilloma virus (HPV), which has been implicated as an important causative agent of cervical cancer, become a research priority. The authors assume a mortality rate of 5 per 100,000 population for cervical cancer; with a global estimate of 280,000 deaths per year in 1984, compared with the estimated 500,000 to 2.3 million adult deaths caused by acquired immunodeficiency syndrome (AIDS) per year for the period 1992 to 2000. Hermonat had shown earlier that nonoxynol–9 was inactive in vitro against bovine papilloma virus, a virus closely related to HPV. The authors argue that the protection against cervical cancer attributed to spermicides may be due to some other factor or confounding effect. They recommend that compounds that are candidates for use as vaginal microbicides be screened for activity against bovine papillomavirus, and they call for a systematic search to identify a compound active against HPV that could be used as a component of a vaginal microbicide.

IV.B–21
HIV Prevention: The Need for Methods Women Can Use.

Form: Commentary.
Author: Stein, Z. A.
Source: American Journal of Public Health. 80(4):460–462, April 1990.

Published Abstract: Efforts to prevent heterosexual transmission of HIV infection have thus far focused on modifying sexual behaviors and the use of condoms. While the experience of family planners, particularly in those countries most threatened by heterosexual HIV transmission, has shown that the most effective measures of pregnancy prevention have relied on women, little attention has been given to barriers to HIV transmission that depend on the woman and are controlled strictly by women. Tactics that interrupt transmission of the virus should be considered in their own right and separated from those that interrupt pregnancy. Greater emphasis is urged for research on preventive methods women could use, including the possibility of a topical virucide that might block transmission through the vaginal route.

IV.B–22
Commentary: The Double Bind in Science Policy and the Protection of Women From HIV Infection.

Form: Journal Article.
Author: Stein, Z. A.
Source: American Journal of Public Health. 82(11):1471–72, November 1992.

Published Abstract: None.
Annotators' Abstract: The author poses a key public health question: What counsel should women be given to protect themselves from sexually transmitted diseases (STDs) and human immunodeficiency virus (HIV)? The message to women could be first to persuade their male sex partners to use condoms; if their partners do not comply but the choice is still to have sex, then the women should use a spermicide. The author uses hierarchical messages to address the problems. The author states that despite problems associated with spermicides, from irritation to ulcers, no literature has suggested that spermicides increase STDs; therefore, in modest dosage and under normal circumstances, the benefit probably outweighs the theoretical possibility of increasing risk, and women should be so counseled. More research is called for to determine whether some spermicides are harmful and, if so, under what circumstances.

IV.B–23
Acceptability of Dual Method.
Author: Steiner, M.; Joanis, C.
[See abstract III.A–32.]

IV.B–24
Vaginal Microbicides for Preventing the Sexual Transmission of HIV.
Author: Stone, A.; Hitchcock, P. J.
[See abstract III.A–34.]

IV.B–25
Scientists Zero In on New HIV Microbicides.
Author: Voelker, R.
[See abstract IV.A–34.]

IV.B–26
The Potential of Nonoxynol–9 for the Prevention of HIV Infection Reconsidered.

Form: Journal Article, Editorial.
Author: Wittkowski, K. M.
Source: AIDS. 9(3):310–311, 1995.

Published Abstract: None.
Annotators' Abstract: This editorial reviews data on the use of nonoxynol–9 (N–9) in the prevention of HIV and responds to an article by Elias and Heise (see IV.B–4). The author concluded that findings from other studies (see Feldblum et al., II.C.ii.a–3) suggest that minor abrasions of the vaginal mucosa that increase the risk for HIV transmission may be compensated for by the possible protective effect of N–9. The author concludes that N–9 should be recommended as one of many strategies for reducing the risk of HIV transmission under certain conditions. These conditions include circumstances in which contraception is acceptable or desired, the average frequency of intercourse is less than once a day, hygienic conditions are available, the dose of N–9 does not exceed 250 mg, N–9 is discharged, and women are advised to see a doctor if irritation occurs.

IV.B–27
Barrier Contraceptives and Spermicides: Their Role in Family Planning Care.
Author: World Health Organization.
[See abstract III.A–36.]

IV.B–28
Joint Statement: Contraceptive Methods and Human Immunodeficiency Virus (HIV).

Form: Monograph.
Author: World Health Organization.
Source: Geneva, Switzerland, World Health Organization, 2 pp., June 1987.

Published Abstract: None.
Annotators' Abstract: The need for research on the possible interactions between contraceptive methods and human immunodeficiency virus (HIV) infection were discussed by participants in a June 1987 joint meeting of the World Health Organization (WHO) Special Program on Acquired Immunodeficiency Syndrome (AIDS) and Special Program of Research, Development of Research Training in Human Reproduction. Theoretical interactions between contraceptive methods and HIV infection were discussed; bu because data were insufficient, no firm conclusions were drawn. Participants recommended that WHO conduct additional research on the following topics: the influence of oral contraceptives and IUDs on susceptibility to HIV infection; infectiousness of HIV–infected women; the development and course of HIV–related illness; the mechanism of HIV transmission and modification by contraceptive methods; and the influence of pregnancy on the development and courses of HIV–related illness. They also advised that condoms always be used when there is any risk of HIV infection.

IV.B–29
Prevention of Sexual Transmission of Human Immunodeficiency Virus.

Form: Monograph.
Author: World Health Organization.
Source: Geneva, Switzerland, World Health Organization, WHO AIDS Series, No. 6, 27 pp., 1990.

Published Abstract: None.
Annotators' Abstract: This report summarizes World Health Organization guidelines for public health authorities, health care providers, HIV–infected persons, sexual partners of persons who are seropositive, and the general public. The specific steps recommended for HIV–infected persons are to discuss their seropositivity with current and former sexual partners; to adopt safe sex practices that do not involve the exchange of body fluids; and, for infected females, to avoid pregnancy. The general public can reduce the risk of acquiring HIV by carefully selecting sex partners (avoiding sexual relations with strangers, prostitutes, or intravenous–drug users); reducing the number of partners; and avoiding sexual practices that involve the sharing of semen, vaginal, and cervical secretions if the partner's drug–taking and sex histories are unknown. Appendices to this pamphlet discuss the complex medical, logistical, social, legal, and ethical issues raised by partner notification, and the growing evidence that sexually transmitted diseases, particularly those that produce ulcers, may enhance the risk of HIV infection.

IV.B–30
Report of the Strategic Meeting on Development and Accessibility of Preventive Technology Including Vaginal Microbicides for HIV/AIDS.

Form: Monograph.
Author: World Health Organization.
Source: Paris, France, World Health Organization, September 15–16, 1994.

Published Abstract: None.
Annotators' Abstract: This report states that female–controlled barriers to HIV (and possibly to other sexually transmitted diseases), such as vaginal microbicides, are urgently needed and may be developed faster than a vaccine. Impediments to development and accessibility include the fact that most products have been—and are most likely to be—developed in the private sector. Research and development objectives, accessibility objectives, and ethical principles are discussed.

IV.B–31
A Practical Method to Reduce HIV Risk in African Women.
Author: Ziegler, J. L.
[See abstract III.A–37.]

IV.B–32
[Real and False Risk of Local Contraception: Spermicides and the Diaphragm.] [French.]
Author: Zufferey, M. M.
[See abstract IV.A–35.]

IV.B–33
Female–Controlled Methods to Prevent Sexual Transmission of HIV.
Author: Elias, C.; Coggins, C.
[See abstract III.A–14.]

IV.C. Overviews–Compilations.

IV.C–1
Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989.

Form: Book Chapter.
Author: Alexander, N. J.; Gabelnick, H. L.; Spieler, J. M. eds.
Source: New York: Wiley–Liss., 440 pp., 1990.

Published Abstract: None.
Annotators' Abstract: The editors have compiled papers presented at the 1989 International Workshop. The papers addressed the principal risk factors in the heterosexual transmission of human immunodeficiency virus (HIV); how sexual behavior changes that risk; the biology and pathogenic mechanisms of retroviruses; animal models of the mechanisms and prevention of the heterosexual transmission of HIV; the impact of contraceptive methods; and priorities for future research.

IV.C–2
HIV and Contraception: Research Priorities. IN: Heterosexual Transmission of AIDS: Proceedings of the Second Contraceptive Research and Development (CONRAD) Program International Workshop, Norfolk, Virginia, February 1–3, 1989.

Form: Conference Proceedings.
Author: Hodgen, G. D.
Source: New York: Wiley–Liss., pp. 415–418, 1990.

Published Abstract: None
Annotators' Abstract: The 1989 International Workshop established priorities in HIV and contraceptive research: (1) elucidation of the vectors and routes of heterosexual HIV transmission; (2) testing of the feasibility of contraceptive methods that limit the heterosexual transmission of HIV; (3) evaluating virucidal activity of spermicides containing nonoxynol–9; (4) evaluating alternative spermicidal agents that have good virucidal efficacy; (5) developing animal models to study heterosexual HIV transmission; (6) elucidating risk factors associated with different contraceptive methods; and (7) evaluating failure rates of contraceptive methods in populations with high rates of HIV transmission.

IV.C–3
Reducing the Risk of HIV Infection Among South African Sex Workers: Socioeconomic and Gender Barriers.

Form: Journal Article.
Author: Karim, Q. A.; Karim, S. S.; Soldan, K.; Zondi, M.
Source: American Journal of Public Health. 85(11):1521–25, November 1995.

Published Abstract: Objectives: The social context within which women engaged in sex work at a popular truck stop in South Africa placed at risk of human immunodeficiency virus (HIV) infection and the factors that influence their ability to reduce their risk, were assessed. Methods: Using qualitative and quantitative techniques, an elected sex worker from within the group collected all data. Results: Given the various pressing needs for basic survival, the risk of HIV infection is viewed as one more burden imposed on these women by their lack of social, legal, and economic power. Violence, or the threat thereof, plays an important role in their disempowerment. In the few instances in which sex workers were able to insist on condom use, it resulted in decreased earnings, loss of clients, and physical abuse. Conclusions: Recommendations to reduce the sex workers' risk for HIV infection include negotiation and communication skills to enable them to persuade their clients to use condoms; development of strategies through which they can maximally use their group strength to facilitate unified action; and accessibility of protective methods they can use and control, such as intravaginal microbicides.

IV.C–4
Update on Topical Microbicides.

Form: Report.
Author: National Institute of Allergy and Infectious Disease, National Institutes of Health.
Source: National Institutes of Health, Bethesda Maryland, 1995.

Published Abstract: None.
Annotators' Abstract: This report contains information on a number of topics relating to the microbicides initiative at the National Institutes of Health. Protocols for studies, requests for proposals and grants, and scientific and preclinical considerations are discussed.

IV.C–5
Critical Issues in Reproductive Health and Population: A Report of a Meeting Between Women's Health Advocates, Program Planners, and Scientists, New York and Washington, D.C., 3–12 May 1994.

Form: Report.
Author: Voelker, R.
Source: JAMA. 273(13):979–980, April 5, 1995.

Published Abstract: None.
Annotators' Abstract: This report summarizes two meetings that addressed microbicidal development, laboratory issues, research priorities, and prevention strategies.

IV.C–6
The Potential Contribution of Family Planning Programs to AIDS Prevention in Developing Countries.

Form: Book Chapter.
Author: Williamson, N. E.
Source: IN: International Health in the 1990s: Directions in Research and Development, NCIH Southern Regional Conference, Chapel Hill, North Carolina, October 29–31, 1987. Selected Proceedings, Heffernen, M., ed. Washington, D.C.: National Council for International Health, pp. 97–101, April 1988.

Published Abstract: None.
Annotators' Abstract: This report summarizes a conference on the potential contribution of family planning programs to the prevention of HIV infection. Several recommendations were discussed: (1) in developing countries with the potential for a serious AIDS problem, governments need a strategy for using organizational resources; (2) family planning organizations can be a valuable resource, yet their approaches must be modified considerably to influence the AIDS epidemic; (3) family planning programs generally have experience in educating people about condoms and spermicides and in distributing condoms and spermicides, both of which have a protective effect against the AIDS virus; (4) because the behavioral changes required to prevent AIDS are more demanding than those to prevent pregnancy, educational efforts will need to be even more intensive; (5) the population that must be encouraged to use barrier methods of contraception is far broader than the clientele of a typical family planning program, and includes men, persons who have been sterilized, pregnant women, subfecund couples, and women past childbearing age.

V. Policy.

V–1
Technical Advisory Group, Agency for International Development Acquired Immunodeficiency Syndrome (AIDS) Program.

Form: Book.
Author: Sponsored by the Agency for International Development, AIDSTECH, AIDSCOM.
Source: Research Triangle Park, North Carolina, FEII, 120 pp. 1081–1201. February 17, 1989.

Published Abstract: None.
Annotators' Abstract: This report discusses the role of USAID in AIDS research in developing countries. USAID–funded research is intervention oriented, with priority given to operations research in behavioral change, condom promotion, and blood screening for HIV. The AIDSTECH program research includes a focus on the sexual transmission of AIDS (control of sexually transmitted diseases, condom use, anthropologic studies of high–risk behavior groups, the efficacy of spermicides, and the cost–effectiveness of interventions). The report reviews progress of ongoing projects. Research plans of other agencies were presented at the meeting.

V–2
New IMAP Statement on the Acquired Immunodeficiency Syndrome (AIDS).

Form: Journal Article.
Author: International Planned Parenthood Federation; International Medical Advisory Panel.
Source: IPPF Medical Bulletin. 24(6):1–3, 1990.

Published Abstract: None.
Annotators' Abstract: This statement revises two earlier statements on human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) issued in November 1990. Epidemiology, transmission, diagnosis, prevention, information, and education are covered, and information on the prevention of occupational transmission for health care workers is given. The statement notes that spermicides alone should not be recommended and urges maintenance of current breast–feeding policies.

Appendix A.

Report of the Strategic Meeting on Development and Accessibility of Preventive Technology Including Vaccines and Microbicides for HIV/AIDS

Paris, 15–16 September 1994

Introduction

The impact of HIV/AIDS on individuals, families and society is so devastating—especially in the developing world, where 90% of HIV infections occur—that it lends special urgency to the search for effective and accessible products for prevention. For example, the search for a vaccine against HIV must not be allowed to stagnate, no matter how long, complex and frustrating the endeavor, for immunization is probably key to bringing the pandemic under control. Female-controlled barriers to HIV (and possible other sexually transmitted pathogens) such as vaginal microbicides are urgently needed and may lend themselves to faster development than a vaccine.

Situation analysis

Development

The scientific community has made great strides in understanding the etiology and pathogenesis of AIDS. That scientific understanding, derived mainly through research conducted in academic institutions, industry and public research agencies around the world, has provided the basis for the development and improvement of antiviral drugs, vaginal microbicides and drugs against opportunistic infections. Likewise, a first generation of candidate vaccines has been brought to Phase I/II clinical trials, although it is not yet known if these vaccines are effective in protecting against HIV infection.

Additional research is badly needed to improve existing preventive products and to manufacture and test new ones. It is therefore a matter of concern that development efforts in the private sector may be stagnating, especially as regards vaccines. As explained below, major barriers are inhibiting the development, evaluation and marketing of preventive technology, especially products intended for developing countries which have limited commercial potential in the industrialized world.

Accessibility

What are the prospects for ensuring access to future products, including vaccines? A glance at history is instructive: from initial approval to large-scale distribution in developing countries, it took around 15 years for the polio vaccine and some 15–20 years for the measles vaccine. The original plasma-derived hepatitis B vaccine was licensed over a decade ago, yet large-scale distribution in developing countries is just starting. This pace would be unacceptable for the galloping HIV pandemic. Clearly, we cannot afford to repeat history.

Barriers to development and accessibility

Any analysis of the barriers to development and accessibility must begin with the observation that most products have been and are likely to be developed by the private sector. Industry has a mission to develop new products, but understandably those products must be profitable. Under these circumstances, what are the barriers that a pharmaceutical company might perceive when developing business strategies for HIV/AIDS prevention products? From numerous national and international meetings organized with industry on this subject, there is general consensus regarding at least the following barriers:

- Scientific uncertainty: there is still insufficient understanding of pathogenesis and of how to block HIV transmission and infection;
- Intellectual property: given the history of research into HIV and related technology, there is concern over lack of clarity or competing claims regarding patent rights, or curtailment of the period of protection;
- High development costs: clinical trials for preventive products tend to be expensive, given the need for long follow-up and large sample sizes even in areas of high HIV incidence;
- Geographically-specific products: products needed in some parts of the world may not have a market elsewhere;
- Liability: litigation over alleged adverse effects is a major concern, especially in some markets. This is a problem especially for preventive products such as vaccines and microbicides;
- Market size: especially for preventive technology, there is uncertainty about the number of people who will buy a product;
- Pricing: industry may anticipate pressure e.g. from the public sector or consumer activists to lower prices, especially for publicly mandated vaccines requiring universal coverage. Differential pricing for developing countries might threaten the prices set for developed country markets; and
- Disincentives to entering developing country markets: these include insufficient international regulatory harmonization, inadequate distribution systems, and the risk of parallel imports, counterfeiting and piracy.

Impressive efforts have been undertaken by several academic and public sector organizations, both national and international, to overcome these barriers in collaboration with industry. Meetings with industry have been organized, including by WHO and the United Nations Development Programme (UNDP); the National Institutes of Health, the Institute of Medicine and the Department of Health and Human Services in the USA; and the Foundation Marcel Merieux and the Rockefeller Foundation. Through these interactions, academic and public-sector organizations and industry have attempted to address not only the disincentives to product development but also the barriers to ensuring access to new products.

Progress has nevertheless been far from what is needed. The Paris AIDS Summit offers a unique opportunity to harness political momentum toward the twin goals of HIV product development and accessibility.

Priorities for action

The Paris AIDS Summit could endorse the following principles and national priorities and launch the global initiative outlined below.

Basic principles:

1. The scale of human suffering caused by HIV/AIDS and the rapid expansion of the global epidemic lend special urgency to prevention, especially in the developing world where 90% of infections occur. The search for vaccines, microbicides and other preventive technology must therefore be speeded up. Vaccines have been the keystone of public health success against other infectious diseases, such as smallpox and poliomyelitis. Vaginal microbicides, which are likely to take less time to develop, are urgently needed as a

female-controlled barrier to the sexual transmission of HIV.

2. Billions of dollars will be lost to the world economy because of the pandemic, owing to health care costs and the far greater indirect costs resulting from the illness and death of millions of young and middle-aged adults. Public financing of an initiative to accelerate the development and accessibility of vaccines, vaginal microbicides and other preventive technology is thus a sound economic investment.

3. Because of the formidable and in some respects unique (scientific and market) barriers to developing HIV preventive technology, conventional research and development models will not suffice to meet the global challenge of the epidemic. Nor will traditional approaches to broadening the accessibility of new products in developing countries. Bold vision is needed to come up with new models of action, based on international cooperation, solidarity and collaboration with industry, that will not duplicate existing efforts. By building an innovative partnership involving the public and private sectors, governments and communities, and developed and developing countries alike, the world can accelerate the development and accessibility of preventive HIV technology through a sharing of the financial, political and human risks and benefits.

4. Research on preventive technology must be conducted according to the guidelines established by the Council for International Organizations of Medical Sciences (CIOMS) and in a way that is sensitive to local circumstances. Such research also needs to be carried out in partnership with the population concerned (e.g. through its community-based groups) and with local scientists, so as to strengthen local autonomy and research capability.

5. As soon as a safe and effective preventive product is developed, every possible effort must be made to ensure that it is accessible to all those who need it.

6. While biomedical technology may be key to bringing the pandemic under control, there must be no let-up in efforts to inform and educate people about safe behaviour, provide them with condoms, and ensure treatment of other sexually transmitted diseases (STDs). Behaviour change and STD treatment interventions are a necessity for all populations, particularly those in whom new preventive technology is being tested.

National priorities

1. Governments should maintain at least their current level of commitment to HIV/AIDS research and allocate resources commensurate with the epidemic’s status as one of the world’s most urgent public health problems.

2. Governments should help to identify and resolve product liability issues that hamper the development of new HIV preventive products.

3. Governments should accelerate efforts towards international harmonization for product licensing/registration.

4. Governments should promote the availability of effective products as soon as they are developed, in particular by reducing tax and import duties.

5. Governments should create the necessary conditions for working in partnership with NGOs, community-based organizations and people living with HIV/AIDS to define and implement these priorities.

Global initiative

Recognizing the magnitude and spread of HIV infection and the difficulties inherent in developing safe, effective and usable prevention technologies and making them accessible, the Paris AIDS Summit could call for a new initiative with a mandate to accelerate the development and worldwide accessibility of HIV preventive technologies, particularly vaccines and vaginal microbicides. In anticipation of the forthcoming joint and cosponsored UN programme on HIV/AIDS, the Summit could call on WHO to develop this initiative in partnership with other international organizations, governments, private industry, communities, and nongovernmental organizations including foundations, scientific institutions and representatives of persons with HIV/AIDS, from developed and developing countries alike, ensuring a balanced representation of all interests. Preparation of a global, unified plan could begin immediately following the Summit.

Research and development objectives

The initiative would accelerate and fill critical gaps in current research and development of HIV preventive technologies, particularly vaccines and vaginal microbicides:

- Through partnership between the public and private sectors;
- By sharing risks and benefits, ensuring commercial viability of products, and otherwise minimizing disincentives to product development;
- By simultaneously exploring a number of different leads or technologies; and
- By promoting innovative product-oriented research and development projects entailing calculated scientific and financial risks.

Accessibility objectives

The initiative would ensure accessibility of newly developed products by: - linking public and private sector funding of research and development in a manner that assures public sector access to new products, and hence their rapid accessibility to developing countries, without threat to their commercial viability; - reinforcing distribution mechanisms in developing countries, using the expertise of community-based and other effective channels where possible; and - harmonizing regulatory standards.

Ethical principles

The initiative would be governed by the following ethical principles:

- Internationally recognized ethical principles, including confidentiality and free and informed consent, should be universally applied to clinical research;
- Clinical research should be designed and implemented in a way that is sensitive to local circumstances, including the broad socioeconomic development needs of local populations;
- Populations in which clinical trials are conducted should have access both to proven candidate technologies and to the health care services required for their delivery; and
- International research trials conducted in developing countries should reinforce national research capability.

Appendix B.

SPECIAL REPORT

Recommendations for the development of vaginal microbicides

The International Working Group on Vaginal Microbicides*

Vaginal microbicides are products for vaginal administration that can be used to prevent HIV infection and other sexually transmitted diseases (STD). We recognize two potential sources of vaginal microbicides: existing spermicides and new products (new products may or may not be spermicidal). This document is meant to serve as a general guide for development and evaluation of existing and new products. For new products, preclinical studies will be required. Depending upon indication, *in vitro* activity against HIV, target STD, and sperm should also be assessed. Compatibility with barrier method materials should also be evaluated. The physical-chemical properties of the active agent and the clinical formulation should be assessed. Animal studies should be conducted to assess its safety and predict dosing; use of various models to assess local toxicity is indicated and microbicidal activity of the product may be evaluated if appropriate models are available. Carcinogenicity testing and segment III reproduction studies (perinatal and post-natal studies in rats) may be performed concurrently with Phase III clinical trials. All vaginal microbicides, including existing spermicides and new products, should be clinically evaluated for safety and efficacy. Safety studies are necessary because irritation of vaginal and cervical mucosae has been recently associated with spermicide use and those lesions might increase HIV transmission. Efficacy studies to assess prevention of HIV infection and/or STD, depending upon the product indication, should then be conducted with products that have been evaluated for safety and appear to be non-toxic to tissue. For spermicidal microbicides, contraceptive efficacy studies will be needed.

AIDS 1996, 10:UNAIDS1-UNAIDS6

Keywords: HIV prevention, sexually transmitted disease prevention, vaginal microbicides

Introduction

Heterosexual transmission of HIV is a serious public health concern, as it accounts for about three-quarters of all HIV-1 infections worldwide. Globally, there are currently three men infected for every two women, but by the year 2000 it is projected that number of new infections among women will be close to that among men [1]. While condoms, when used consistently and correctly, are effective in preventing the sexual spread of HIV, there is an urgent need for methods women can use for HIV prophylaxis, such as vaginal microbicides [2]. Vaginal microbicides are products for vaginal administration that can be used to prevent HIV infection

From the International Working Group on Vaginal Microbicides, c/o UNAIDS, Geneva, Switzerland. *See Appendix for contributors.

Note: The proposals in this document were endorsed by consultants to and members of the International Working Group on Vaginal Microbicides, but do not necessarily reflect the policies of their respective agencies and/or organizations.

Requests for reprints to: J. Perriens, Policy, Strategy and Research, UNAIDS, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland; or P. Hitchcock, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Solar 3A21, Bethesda, MD 20892; or A. Stone, Medical Research Council, 20 Park Crescent, London W1N 4AL, UK.

ISSN 0269-9370

and/or other sexually transmitted diseases (STD). An ideal vaginal microbicide would be safe and effective, and also tasteless, colourless, odourless, nontoxic, stable in most climates, and affordable. Currently available spermicides are being clinically evaluated for prevention of infection because their active ingredients — all surfactants such as nonoxynol-9, octoxynol-9, menfegol, benzalkonium chloride or chlorhexidine — have been shown to have antiviral and antibacterial activity *in vitro*. Among the new classes of vaginal microbicides, some products are not spermicidal and may not interfere with procreation: for example, inhibitors of virus absorption, defensins and inhibitors of HIV reverse transcriptase [3-6].

The International Working Group on Vaginal Microbicides (IWGVM) was formed in November 1993 at a meeting held at the World Health Organization (WHO), Geneva, Switzerland. The goal of the IWGVM is to facilitate the development, production, and distribution of safe, acceptable, effective, and affordable vaginal microbicides to prevent HIV infection and other STD. The working group members, experts in relevant scientific areas from governmental and non-governmental agencies, meet regularly to facilitate communication, consultation, and collaboration on scientific advances and technical problems in microbicide development, and to identify needs and opportunities to promote product development.

The present document outlines the guidance the IWGVM has developed on the evaluation of vaginal microbicides.

Preclinical considerations

This section presents steps to be considered in preclinical development of new vaginal microbicides for the prevention of HIV and STD. It is less relevant to the evaluation of existing spermicides as vaginal microbicides. For example, in the United States, the Food and Drug Administration (FDA) does not require pharmacology/toxicology studies for evaluation of nonoxynol-9 and octoxynol-9 as spermicides, and perhaps as vaginal microbicides [7]. In Europe and Japan, regulatory authorities might rule similarly for approved spermicides. However, it might be wise to do some of the tests proposed in this section with spermicidal products to avoid toxicity problems in human studies and to improve prospects for developing a safe, effective microbicide. Indeed, several currently marketed spermicidal products have been associated with genital mucosal lesions [8-11].

The preclinical guidance provided here is a list of studies which may be valuable and performed prior to, or concurrently with, clinical studies. Since candidate products will have different active agents with unique mechanisms of action and formulations, preclinical approaches will have to be tailored for the specific product. The precise studies that will need to be performed will also depend on several factors including (1) the indication for which the product will be tested and marketed, and (2) the regulatory requirements of the host/sponsoring country. Therefore, a product sponsor should contact regulatory agencies about specific requirements for approval of its product as soon as its potential has been delineated.

In vitro activity and safety

The tests described in Table 1 are designed to obtain information regarding the products' potential for prevention of HIV and STD. If the product indication is for the prevention of HIV infection, *in vitro* assays will include a variety of HIV strains (both laboratory-adapted and clinical isolates). Since the precise mechanism of mucosal transmission of HIV is unknown, tests for evaluating prevention of cell-associated HIV transmission are also recommended. It is desirable that an agent be evaluated for activity against HIV and other STD regardless of its intended HIV indication since a clinical outcome of HIV prevention may be achieved by the prevention of other STD [12,13]. Similarly, data on the effect of the agent on lactobacilli as a surrogate for normal vaginal flora is desirable.

Table 1. Recommended tests for *in vitro* activity*

Activity against HIV
- **M** Laboratory-adapted HIV virus in T-cell lines
- **M** Laboratory-adapted HIV virus in peripheral blood mononuclear cells
- **M** Clinical HIV isolates (depending upon the microbicide and the mechanism of action, it may be appropriate to include drug-resistant isolates)
- **M** Activity against cell-associated virus
- **M** Antiviral activity in semen and, if possible, vaginal fluids or in an *in vitro* system that is physiologically appropriate

Activity against other sexually transmitted pathogens
- **M** *Neisseria gonorrhoeae*
- **M** *Chlamydia trachomatis*
- **M** *Haemophilus ducreyi*
- **M** *Trichomonas vaginalis*
- **M** Herpes simplex virus

Activity against other vaginal organisms
- **M** *Lactobacillus crispatus*
- **M** *Candida albicans*

* Tests should be performed on active agent and clinical formulation; if the microbicide contains more than one active agent, each must be tested separately.

As vaginal microbicides should be compatible with other methods, such as the male or female condom used to prevent HIV and STD transmission, it is suggested that both the active ingredient and the final formulation be evaluated for compatibility with latex, polyurethane or other physical barrier materials early on during preclinical development.

In vitro mutagenesis studies can be done in parallel with Phase I clinical studies, and should include gene mutation tests, tests for chromosomal abnormalities primary and DNA damage assays.

Physical-chemical considerations

Clinical formulations must be produced under good manufacturing practices. The properties of the active agent should be known. Well-characterized analytical methods to detect and measure the physical-chemical properties of the active agent are essential for product development. For example, quantitative analytical methods will be needed to determine drug diffusion and potential for systemic absorption of the active agent, and to meet the Standard Chemistry Requirements (Chemistry, Manufacturing, and Control section of the Investigational New Drug application to the FDA in the USA and similar requirements of regulatory bodies elsewhere.)

As the combination of the active agent and a delivery vehicle may result in alterations in physical-chemical properties and microbial activity, it is recommended to assess the stability (real and accelerated time) of both clinical formulation and
vehicle alone, to do formulation release studies (i.e., the kinetics of release of active agent from solid and semi-solid formulations), and to assess *in vitro* activity against the target pathogens, if possible, in comparison with active agent alone.

Animal Studies

Due to the potential for increased HIV transmission in the presence of significant cervical/vaginal inflammation and ulceration, it is recommended that the active agent and the clinical formulation of the product be tested in a rabbit vaginal irritation model (standard 10-day application of active agent and/or preclinical formulation) early in the development process. A 4% nonoxynol-9-containing spermicidal gel should be used as a positive control. If significant irritation occurs, termination of product development may be warranted.

In addition, systemic absorption and the toxicity of the formulation to the rectal mucosa, pubic and other skin areas should be assessed in animal models. Oral toxicity studies, and gross necropsy or more specialized studies, if warranted (including penile irritation and absorption in male rabbits) may be performed concurrently with or after Phase I clinical studies depending upon the topical microbicide. Systemic toxicity studies in one species with single dose administration, hypersensitivity and photosensitivity studies, and segment I reproductive toxicology (spermicidal activity) are required prior to Phase I, and segment II reproductive toxicology studies (standardized tests in two animal species) may be performed subsequent to Phase I studies in humans [14].

Toxicology studies in a rodent and non-rodent species (possibly concurrent with clinical trials) with duration equal to intended duration of clinical studies (up to 12 months) should be performed. Pharmacokinetics data (serum drug levels, maximum concentration, area under the curve, tissue distribution and metabolite profiles) should be presented and compared to human data. If Phase I trials establish that the drug is absorbed in humans and the mucosal route of delivery in animals cannot achieve much higher blood levels than those seen in Phase I, a 1-3 month toxicity study during which the clinical formulation is given parenterally or orally may be required to identify all potential toxicities.

If possible, animal model data on the product's potential efficacy should be obtained. Examples of animal models to be considered are listed in Table 2.

Table 2. Examples of animal models for testing the efficacy of clinical formulations against HIV and sexually transmitted diseases (STD).

HIV
- **M** Simian immunodeficiency virus in macaques
- **M** Feline immunodeficiency virus in cats

STD
- **M** Genital herpes in guinea pigs

- **M** *Chlamydia trachomatis* in mouse or primate
- **M** *Haemophilus ducreyi* in rabbits
- **M** *Treponema pallidum* in rabbits
- **M** Human papillomavirus in nude mice
- **M** Rabbit papillomavirus model

Newer models, such as the mouse herpes simplex virus genital infection models, are presently under development and may be considered.

Carcinogenicity testing is necessary, but may be performed concurrently with Phase III clinical trials. Such testing should involve two animal species (rats and mice), and intra-vaginal administration for up to 2 years at maximum tolerated dose. Segment III reproduction studies (perinatal and post-natal studies in rats) can be performed concurrently with Phase III clinical trials [14].

Clinical considerations

Like all clinical trials, trials on vaginal microbicides should be conducted in accordance with the current version of the Declaration of Helsinki and the Good Clinical Practice guidelines applicable in the country where the trial will take place [15]. In particular, the studies must be ethically sound and be reviewed in advance by an institutional (ethical) review board or other appropriate group, employ informed consent, assure confidentiality, and be monitored for the completeness and accuracy of study data. A standardized approach to collecting all clinical data, administering subject interviews and analyzing data should be used. Laboratory tests should be conducted in laboratories with proper quality assurance procedures. A Data and Safety Monitoring Board (DSMB) composed of a group of physicians, epidemiologists, statisticians and ethicists should oversee the conduct of all long-term clinical trials. The DSMB should review this study at intervals specified in the protocol and advise the sponsors on modification or termination of the trial according to rules for termination of the study defined beforehand.

Use of currently available spermicides or new vaginal microbicides may cause changes and even lesions of the genital mucosa [8-10]. Not knowing what role, if any, these play in the transmission of HIV and STD, the IWGVM believes that information on the status of the genital mucosa must be collected during both safety and efficacy studies on vaginal microbicides. Because changes in genital mucosa may occur independently of symptoms, assessment of the genital mucosa should be by objective methods, such as vaginal speculum examination, while irritation/inflammation should be assessed in Phase I and II studies using colposcopy.

Community-based organizations should be involved as much as possible in the design and implementation of the studies, especially with regard to its feasibility and acceptability, including establishment and maintenance of the appropriate clinical and social infrastructure for the trial.

Design and implementation of Phase I, II and III clinical trials

Phase I trials

The main objectives of Phase I trials are usually (1) to gather initial information on the incidence and extent of toxicity for a product that has never been used in humans, (2) to obtain data on the pharmacokinetics of the product, and (3) to aid in the selection of a dose for subsequent studies. Open-label studies, some probably with dose escalation, in a small number of healthy, non-pregnant female volunteers not at risk of pregnancy or STD, who would use the study drug for one to a few days (per dose-escalation level) should be adequate. If the main objective of the study is to gather safety information, colposcopy should be used to assess the status of the genital mucosa. Systemic toxicity of the product should be assessed by appropriate laboratory tests. Volunteers in early Phase I studies of a new product should abstain from vaginal intercourse thereby avoiding its potential confounding effect on the incidence of genital lesions.

Phase II trials: further safety studies and pilot studies

After Phase I studies are completed, the product's safety should be confirmed in larger studies among healthy, non-pregnant female volunteers not at risk of pregnancy or STD. Ideally this study should be a randomized, double-blind comparison of the new product to placebo (i.e., the product formulation without its active ingredient) or to a reference product on one hand, and to an untreated group on the other. Use of a placebo group would enable assessment of the safety characteristics of the vehicle; this information is critical to future studies. A cross-over design, in which the product, placebo and non-use would be given sequentially, would also be acceptable. However, subject dropouts and the need to include a wash-out period for products with persistent effects limit the utility of this design and should be taken into consideration. Finally, the utility of open-label studies is

limited because findings cannot be compared to the placebo. When participants in Phase II studies have sexual intercourse and lubricated condoms are used, the lubricant should contain no spermicidal products. Study should be designed in collaboration with biostatisticians. The appropriate sample size, duration of the study, and virtually all other aspects of the study design will be effected by many factors, for example, product characteristics, outcome measures, and will require biostatistical expertise.

When the safety of the study drug has been documented in low-risk, healthy women, it is recommended that additional safety studies be conducted in other populations prior to or at the beginning of Phase III studies; safety should be monitored during the Phase III study as well. Examples of other populations of women include commercial sex workers, pregnant women, HIV-infected women, women using reproductive hormones, intrauterine device users, intravenous drugs or crack cocaine users, pre-menopausal or post-menopausal women, and breast-feeding women. Consideration should also be given to an assessment of the product's administration via rectal route. Finally, it is suggested that all clinical studies should be regarded as opportunities to collect data about product acceptability and its ease of use.

Phase III studies

Phase III studies aim to assess the balance between efficacy and toxicity of a new product. For vaginal microbicides, Phase III studies should determine whether the product will prevent heterosexual transmission of HIV and/or other STD depending upon the product among women at high risk of acquiring those infections. The incidence of adverse events (i.e.,potential toxicity) should be assessed to obtain information on the long-term safety of the product. Phase III studies should be randomized, double-blind, controlled trials. Again, the study should be designed with biostatisticians. Phase III studies will need to be sufficiently large to assess the risk and benefits of a product.

Furthermore, inconsistent use of the product, and use of condoms or other interventions such as treatment of incident STD will complicate analyses. As male condoms are the only currently available effective method to prevent heterosexual transmission of HIV, condom use must be recommended and condoms made available to all study participants. In other words, the study design will test whether the microbicide will improve the protection afforded by condom use. If in the future, a vaginal microbicide were shown to be effective in preventing HIV infection, placebo-controlled trials would become inappropriate and new microbicides should be compared to the vaginal microbicide with known efficacy. Phase III studies will also enable an assessment of product acceptability for women and men, compliance with product use, effects on the male partner, and pregnancy rates, if appropriate.

Study populations

Study participants for Phase I and initial Phase II studies should be volunteers at low risk of HIV infection and STD, ideally of reproductive age (i.e., 18-45 years of age). Participants in Phase III studies should be HIV-uninfected women at high risk of acquiring HIV infection and other STD through vaginal intercourse.

Depending on the microbicide being evaluated and study type, women with systemic diseases, women who use other drugs that could modify the pharmacokinetics or the effects of the study product, or women who are pregnant or nursing (unless the product has been demonstrated to be safe for administration in these situations) may need to be excluded from the study. Women presenting with clinically apparent genital infections and/or lesions at enrollment should be treated prior to inclusion. For initial safety studies, the exclusion criteria may need to be more rigorous, and it may be necessary to exclude women with (1) abnormal liver or renal function; (2) a history of genital problems; (3) colposcopic abnormalities; (4) other STD; and (5) continued use of other vaginal products such as douches, tampons, or spermicides (during the study period).

Excluding HIV-infected subjects from participation in Phase III studies may not be possible, mainly for confidentiality considerations. However, these participants will contribute safety information and may contribute to assessment of the products' efficacy against other pathogens. Because of the ease of intravenous or rectal HIV transmission, it is also preferable to exclude women who are intravenous drug users or who frequently and regularly practice anal intercourse. As it is not possible to ensure that the participants will not engage in these high-risk behaviours, it is recommended to quantify

the incidence of high-risk behaviours in Phase III studies.

Study outcomes and their detection

It is recommended that histories on the incidence of vaginal discharge, genital discomfort (including vaginal pain and burning sensations in the vagina and/or the vulva), vaginal dryness, painful urination or intercourse, lower abdominal pain and genital infection be collected in all studies on vaginal microbicides. Reasons for discontinuation should be recorded and adverse events documented.

Toxicity to the genital mucosa should be assessed by objective methods. Colposcopy should be used in initial safety studies. In later studies, vaginal speculum examination may be sufficient, but it is probably wise to monitor local safety with colposcopy in a subset of participants, as recommended for the development of new spermicides [4]. Colposcopic examination should follow the WHO manual for the standardization of colposcopy (available on request from UNAIDS). This manual describes the lesions as ulcers, abrasions, ecchymotic, and petechial haemorrhages, sub-epithelial haemorrhages plus oedema, erythema, oedema, or abnormal vaginal and cervical discharge. Signs of cervical/vaginal dysplasia, neoplasia or metaplasia are not described in the WHO manual but would be recognized by a skilled colposcopist and should also be recorded. In Phase I/II safety studies, the toxicity to the genital mucosa should be evaluated between menses to avoid difficulties assessing the genital mucosa when menses are present.

In studies focusing on the assessment of safety of the product to the genital mucosa the frequency of clinical, gynecological, and colposcopic examinations should be frequent, not less than once every 7-10 days. When genital lesions occur, more frequent examinations may be necessary. Systemic toxicity should be assessed using appropriate laboratory tests, at least at enrollment and at the end of each observation period. Assessment of STD and other genital infections is recommended to exclude them as confounders in the analysis of the data.

In Phase III studies, these evaluations should take place at study enrollment, and at regular intervals (possibly monthly) thereafter, for as long a follow-up period as possible. Currently the populations that would be appropriate for Phase III studies (those with high seroincidence rates) may be difficult to follow. It is anticipated that follow-up will not, in most cases, exceed 1 year, but every effort should be made to improve it by establishment of appropriate infrastructure. Evidence of local toxicity should be sought by pelvic examination (and colposcopy in a subset of participants if possible). Screening for incident HIV infection should be with state-of-the-art laboratory methods, such as third-generation HIV serologic tests, HIV culture, HIV antigen detection and polymerase chain reaction. The diagnosis of STD should be by using state-of-the-art laboratory techniques. Organisms to be considered to measure the incidence of STD include (1) *Trichomonas vaginalis,* (2) *Neisseria gonorrhoeae,* (3) *Chlamydia trachomatis,* (4) *Treponema palllidum,* (5) *Haemophilus ducreyi,* and (6) herpes simplex virus. Compliance with both condom and microbicide use could be assessed with coital log charts and subject interviews. Incidence of anal intercourse and intravenous drug use could be assessed with coital log charts and subject interviews. Incidence of anal intercourse and intravenous drug use during the study should be obtained and recorded. Pregnancies should be determined by testing. If the male partner can be evaluated, genital irritation and infections that are reported should be confirmed if possible.

Handling of participants who develop adverse reactions

Participants should discontinue use of study products immediately when a serious adverse reaction occurs [16].

In Phase I and Phase II studies, study products should be discontinued when genital ulceration occurs. When genital abrasion, petechial haemorrhage, ecchymosis, or subepithelial haemorrhage and swelling occurs, study products should be discontinued if after 24-72 hours of continued study product use the condition worsens.

When in a Phase III study, a genital ulceration occurs, study products may continue but treatment for bacterial causes of genital ulceration (chancroid and/or syphilis) should be given immediately. If the ulcer worsens after 7 days, use of study products should be discontinued, at least until the lesion is cured. When other genital lesions occur, study products should be discontinued if, after 7 days of continued study product use, the condition

worsens. Product use may be resumed after the lesion resolves.

Women who discontinue therapy for any reason should be encouraged to continue follow-up to assess genital irritation, to detect potential toxicity that might arise after cessation of study drug use, and to assess their STD and HIV outcomes for intention-to-treat analyses.

References

1. Mertens TE, Belsey E, Stonebuner R, *et al.:* **Global estimates and epidemiology of HIV-1 infections and AIDS: further heterogeneity in spread and impact.** *AIDS* 1995, 9(suppl A):5259-$272.
2. Stein ZA: **HIV prevention: the needs for methods women can use.** *AM J Public Health* 1990, 80:460-462.
3. Elias C, Heise L: *The Development of Microbicide: A New Method of HIV Prevention for Women. Program Division Working Papers (No. 6).* New York: The Population Council; 1993.
4. Global Programme on AIDS, World Health Organization: *Report on a Meeting on the Development of Vaginal Microbicides for the Prevention of Heterosexual Transmission of HIV.* Geneva: GPA/WHO; 1993. (Document WHO/.GPA/RID/CRD/94.1; 11-13 November 1993).
5. Hitchcock PJ, Claypool L: **HIV and other STD: Working Group Report.** In: *Barrier Contraceptives.* Edited by Mauck C, Cordero M, Gabelnik H, Spieler JM, Rivera R. New York: Wiley-Liss; 1994:353-362.
6. Stone AB, Hitchcock PJ: **Vaginal microbicides for preventing the sexual transmission of HIV.** *AIDS* 1994, 8 (suppl 1):S285-S293.
7. US Food and Drug Administration: *Guidance for the Development of Vaginal Contraceptive Drugs* (27 January 1995). [Clarifications: 8 February 1995]. Washington, DC: US Government; 1995.
8. Niruthisard S, Roddy RE, Chutivongse S: **The effects of frequent nonoxynol-9 use on the vaginal and cervical mucosa.** *Sex Transm Dis* 1991, 18:176-179.
9. Roddy RE, Cordero M, Cordero C, Fortnye JA: **A dosing study of nonoxynol-9 genital irritation.** *Int J STD AIDS* 1993: 4:165-170.
10. Kreiss J, Ngugi E, Holmes K, *et al:* **Efficacy of nonoxynol-9 contraceptive sponge use in preventing heterosexual transmission of HIV in Nairobi prostitutes.** *JAMA* 1992, 268:477-482.
11. Goeman J, Ndoye I, Sakho LM, *et al.:* **Frequent use of menfegol spermicidal vaginal foaming tablets associated with a high incidence of genital lesions.** *J Infect Dis* 1995, 171:16-24.
12. Laga M, Manoka A, Kivuvu M, *et all.:* **Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study.** *AIDS* 1993, 7:95-102.
13. Grosskurth H, Mosha F, Todd J, *et al.:* **Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial.** *Lancet* 1995, 346:530-536.
14. Federal Register Notice: *International Conference on Harmonization — Guideline on Detection of Toxicity to Reproduction for Medicinal Products* (22 September 1994). Washington, DC: US Government; 1994.
15. World Medical Association Declaration of Helsinki. In: *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Geneva: Council for International Organization of Medical Sciences; 1993: 47-50.
16. World Health Organization: *World Health Organization Guidelines on Good Clinical Practice.* Geneva: WHO; 1995. (WHO Technical Report Series No. 850, Annex 3).

Appendix

Contributors to the International Working Group on Vaginal Microbicides

N.J. Alexander (National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA), V. Alexander (Community Family Planning Council, New York, New York, USA), S. Allen (Advances in Health Technology, Washington, DC, USA), L. Dorflinger (Family Health International, Research Triangle Park, North Carolina, USA), A. Duerr (Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA), C. Elias (The Population Council, Bangkok, Thailand), D. Feigal (Division of Antiviral Drug Products, Food and Drug Administration, Rockville, Maryland, USA), E. Gollub (AIDS Coordinating Office, City of Philadelphia, Philadelphia, Pennsylvania, USA), H. Gabelnick (CONRAD Program, Arlington, Virginia, USA), M. Harris (Society for Women and AIDS in Africa, Freetown, Sierra Leone), P.J. Hitchcock (National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland, USA), M. Karam (Global Programme on AIDS, World Health Organization, Geneva, Switzerland), K. Kazempour (Division of Antiviral Drug Products, Food and Drug Administration, Rockville, Maryland, USA), J. Lange (Global Programme on AIDS, World Health Organization, Geneva, Switzerland), J. Perriëns (Policy, Strategy and Research, UNAIDS, Geneva, Switzerland), R. Roddy (Family Health International, Research Triangle Park, North Carolina, USA), P. Rowe (Special Programme for Research, Development and Training in Human Reproduction, World Health Organization, Geneva, Switzerland), Z. Rosenberg (National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA), A. Stone (Medical Research Council, London, UK), P. Stratton (National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA).